Clinical and psychological aspects of cardiovascular risk management in primary care hypertension patients

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Clinical and Psychological Aspects of Cardiovascular Risk Management in Primary Care Hypertension Patients

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Het verschijnen van dit proefschrift werd mede mogelijk gemaakt door de steun van de Nederlandse Hartstichting

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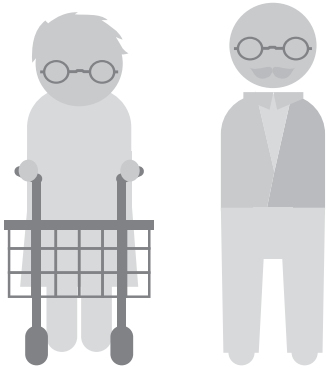
Chapter 1

General Introduction



Hypertension

In the encyclopedia of health and aging, hypertension is described as a *"persistent elevation of arterial blood pressure"*.[1] With aging, the arterial structure and function change, which eventually can result in hypertension.[2] Systolic blood pressure (SBP) increases linearly with increasing age, while diastolic blood pressure (DBP) starts to decrease above the age of 60 years. Both systolic and diastolic blood pressure are associated with increased stiffness of the large arteries.[3]

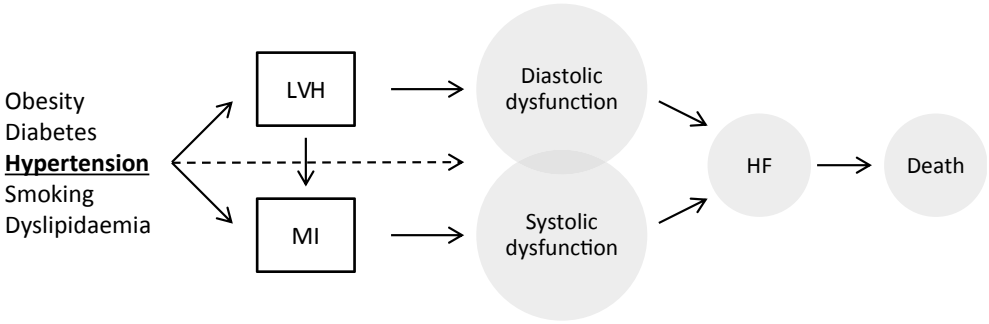
The population is aging and hypertension is observed in the majority of elderly people, which is a major concern for health care. Worldwide, hypertension in the adult population is prevalent in approximately 26%, with the prevalence expected to increase to 29% by 2025.[4] An even higher prevalence with a mean of 44% across six European countries has been reported already in the 1990's.[5] In 2010, in a Dutch population of elderly individuals (60-70 years), hypertension was prevalent in 62% of men and in 55% of women, increasing to approximately 70% for both men and women aged between 70 and 80 years.[6] The Framingham study showed that for adults aged 55 years, the lifetime risk of developing hypertension was 90%.[7]

Hypertension and cardiovascular disease

Hypertension has been defined as a SBP of ≥140 mmHg and/or a DBP of ≥90 mmHg (stage/grade 1 hypertension), while a SBP of ≥160 mmHg and/or a DBP of ≥100 mmHg is defined as stage/grade 2 hypertension according to the American Heart Association (AHA), and the European Society of Hypertension/European Society of Cardiology guidelines.[8,9] Hypertension is a major risk factor for the onset of cardiovascular disease, including coronary artery disease, heart failure, and stroke.[10] A self-reported history of hypertension has been shown to be the most important risk factor for stroke (including all subtypes).[11] However, within the scope of this thesis, we will mainly focus on hypertension in relation to cardiac dysfunction. The risk for ischemic heart disease mortality as well as other vascular mortality increases linearly with increasing blood pressure.[12] The Framingham Heart Study has shown that for individuals with a blood pressure exceeding 160/100 mmHg the lifetime risk for heart failure is approximately two times higher as compared to individuals with a blood pressure of less than 140/90 mmHg.[13] A meta-analysis has shown that for hypertensive patients aged between 40 and 69 years, an increase of 20 mmHg starting at a SPB of 115 mmHg is associated with a twofold increase in cardiovascular death rates.[12] Although other factors also contribute to the development of heart failure, myocardial infarction (MI) is associated with the largest risk for development of heart failure. However, hypertension has the largest population-attributable risk because of its high prevalence.[14] Hypertension

leads to an increased hemodynamic burden on the myocardium,[15] and is associated with MI and changes in the (left) ventricular structure, and may finally evolve into heart failure.[2] As summarized in an overview of Vasan and Levy,[16] hypertension is the most important risk factor for left ventricular hypertrophy (LVH), which in turn may result in left ventricular diastolic dysfunction. Furthermore, LVH is an important risk factor for MI, which is associated with left ventricular systolic dysfunction. Both asymptomatic left ventricular systolic and diastolic dysfunction can evolve into clinical chronic heart failure, which underlines the key role of hypertension in the development of heart failure (figure 1), as well as the importance of early diagnosis and adequate interventions.[16]

Figure 1. Progression from hypertension to heart failure, figure adapted from Vasan and Levy.[16]



LVH, left ventricle hypertrophy; MI, myocardial infarction; HF, heart failure

A review by Allen et al., showed that lowering blood pressure is related to a reduced risk of major cardiovascular events.[17] In case of high blood pressure at 55 years of age, a decrease in blood pressure is associated with a lower lifetime risk for cardiovascular disease (CVD) and/or coronary heart disease (CHD), while an increase of blood pressure beyond this age is associated with an increased lifetime risks for CVD and CHD.[18] Previous research showed that in elderly patients SBP is more predictive of mortality and cardiovascular events than DBP. Therefore, treatment of blood pressure with antihypertensive medication should be directed towards lowering the SBP.[19] In agreement with these findings, in the Dutch guideline on cardiovascular risk management (CVRM) developed by the Dutch College of General Practitioners, generally a target SBP of ≤140 mmHg is advised.[20] However, achieving optimal blood pressure control in hypertension patients in primary care is difficult.[21] A previous study reported adequate blood pressure control between 23% and 38% of hypertension patients in 5 European countries.[21] A Spanish study showed that optimal blood pressure control is achieved in approximately 40% of patients above the age of 65,[22] while a Danish study showed adequate blood pressure control in only 33% of primary care patients,[23] with optimal blood pressure control generally declining with increasing age.[24-26]

Cardiovascular risk management and hypertension

On April 7 2013, the WHO released the report "*A global brief on hypertension*". The prevention and control of hypertension is described as one of the keys to reduce death and disability from noncommunicable diseases.[27] Currently integrated guidelines focusing on CVRM, such as the 2010 American College of Cardiology (ACC) / AHA Guideline for Assessment of Cardiovascular Risk in Asymptomatic Adults, strongly focus on initial assessment of risk factors in apparently healthy individuals in order to prevent CVD.[28] Since 2006, the Dutch unifactorial guidelines on hypertension and hypercholesterolemia have been integrated into one multidisciplinary guideline on CVRM.[29] This guideline focuses on a risk profile using the SCORE criteria[10] - a risk scoring system for use in the clinical management of cardiovascular risk - in which systolic blood pressure plays a major role.[20] The SCORE criteria include systolic blood pressure, gender, age, cholesterol (total or total/HDL ratio), and smoking, in order to calculate a percentage for the estimation of the total cardiovascular risk.[10]

In the Netherlands, during the last decade, large primary care groups have been founded in which general practitioners (GPs) and practice nurses (PN) collaborate according to standardized protocols. There are now around 100 primary care groups operational in the Netherlands, varying in size from 10 to over 200 GPs. PoZoB is an example of a large primary care group (150 GPs responsible for the primary care of 350.000 patients) located in the South-East of the Netherlands. The patient population is predominantly living in a semi-rural area. In 2010, PoZoB initiated a CVRM program in which currently almost 45.000 patients with one or more risk factors for a (primary or secondary) cardiovascular event are prospectively followed by a PN according to a Dutch guideline on CVRM developed by the Dutch College of General Practitioners.[20] The purpose of this CVRM program is to prevent the development of a primary cardiovascular event in high-risk patients according to the SCORE criteria, and to prevent a secondary event in patients with established CVD.[10] The SCORE project used pooled datasets from 12 European countries to construct risk charts which predict the ten-year risk of fatal CVD by using age, gender, smoking, mean cholesterol, and mean SBP.[10] In the CVRM program, patients who meet the SCORE criteria are included. Since hypertension is highly prevalent, especially in the elderly[6], these patients represent a large proportion of the patients included in the CVRM program.

The Dutch guideline on CVRM - applied in the CVRM program of PoZoB - recommends a target SBP of ≤140 mmHg in patients with hypertension below 80 years of age. In patients aged 80 years or older, a target SBP of ≤160 mmHg is recommended, while for type 2 diabetic patients the target SBP is ≤130 mmHg.[20] Lowering blood pressure, also in patients above 55 years of age, is important to reduce the risk of cardiovascular events.[18] However, more information on the status of blood pressure control in Dutch primary care in relation to the current Dutch guideline on CVRM is needed.

Antihypertensive medication

The Dutch guideline on CVRM recommends diuretics as medication of first choice in the treatment of hypertension, with calcium channel blockers (CCB) as second option in case of adverse effects of diuretics. However, angiotensin converting enzyme (ACE) inhibitors as well as angiotensin II receptor blockers (ARBs) are equally effective for the prevention of cardiovascular events as compared to CCBs and diuretics.[30] As a second step, the combination of a diuretic and an ACE-inhibitor can be considered, with replacement by an ARB in case of adverse effects. Third, a combination of a diuretic with an ACE-inhibitor or ARB, and a CCB would be recommended. In case of intolerance to one of the above described antihypertensive medications, a beta-blocker can be considered as a sufficient alternative, although accompanying adverse effects of beta-blockers, which are common, should be taken into consideration.[20]

The role of beta-blockers has been reduced in the current guidelines, because several studies have shown that beta-blockers are less effective in reducing cardiovascular risk.[30] However, beta-blockers are still strongly recommended in patients with prior MI.[20,31] Despite the availability of effective medication, hypertension remains a risk factor for heart failure, which can partly be attributed to inadequate drug prescription and partly to sub-optimal compliance of patients. Persistent use of antihypertensive medication is an important determinant of lowering blood pressure.[32] Therefore, an overview of the current status of blood pressure control in Dutch primary care in relation to the recommendations in the CVRM guideline could provide valuable information.

Screening for cardiac dysfunction

Symptomatic heart failure is generally preceded by asymptomatic cardiac dysfunction or changes in cardiac structure such as LVH.[33,34] Recent guidelines of the ACC and the AHA describe four stages of heart failure, including not only symptomatic but also the preceding asymptomatic stages. Stage A includes patients with only risk factors for the development of heart failure, including hypertension; stage B includes asymptomatic cardiac dysfunction; stage C includes overt heart failure; and stage D represents end-stage heart failure.[33,35] The transition from the asymptomatic stage B to the symptomatic stage C is associated with a sharp (5-fold) decrease in five-year survival,[33] suggesting the importance of early detection of cardiac dysfunction and adequate treatment of risk factors (Table 1).

According to the ACC and AHA 2010 guidelines on CVRM, early assessment of cardiovascular risk can provide a basis for individualized efforts to prevent CVD.[28] A scientific statement from the AHA published in 2008 recommends that future studies should focus on the identification of asymptomatic individuals with left ventricular dysfunction (stage B

heart failure).[36] Furthermore, in the 2011 ACC and AHA expert consensus document on hypertension in the elderly, echocardiography is considered to be a useful tool to evaluate LVH and left ventricular dysfunction in 'selected' elderly persons. However, criteria for this selection are not delineated.[2] In previous studies, echocardiography has been recommended for the detection of both LVH and left ventricular systolic dysfunction in patients at risk for heart failure.[37,38] Moreover, not only LVH, diastolic, and systolic dysfunction are associated with heart failure, but also valvular heart disease and wall motion abnormalities can contribute to the development of heart failure and are related to CHD.[39,40] Echocardiography is seen as the gold standard for confirming a diagnosis and establishing the cause of heart failure.[35,41] The current guidelines on heart failure of the European Society of Cardiology considers echocardiography as a useful tool to assess chamber volumes, ventricular systolic and diastolic dysfunction, wall motion, wall thickness, and valvular function, which are all predictive of heart failure.[41] Therefore, screening of elderly adults with hypertension by means of echocardiography could provide useful information for a treating physician. Although an echocardiogram is a cheap and non-invasive assessment with high sensitivity to detect cardiac abnormalities, it is not routinely used by the GP.[42] Since blood pressure control in (elderly) hypertension patients is generally poor,[21] these patients are likely to be at high risk for heart failure. Therefore, screening hypertension patients for asymptomatic cardiac dysfunction might provide insight into which patients are at higher risk for developing heart failure.

Table 1. Heart failure stages according to the ACC/AHA guidelines, adapted from Hunt et al.[35]

Stage	*Guideline description*	*Including patients with (e.g.):*
A	At high risk for heart failure but without structural heart disease or symptoms of heart failure	Hypertension Atherosclerotic disease Diabetes
B	Structural heart disease but without signs of symptoms of heart failure	Previous myocardial infarction Left ventricle hypertrophy and/or low ejection fraction Asymptomatic valvular disease
C	Structural heart disease with prior or current symptoms of heart failure	Known structural heart disease AND Shortness of breath, fatigue, reduced exercise tolerance
D	Refractory heart failure requiring specialized interventions	Symptoms at rest despite optimal medical therapy Recurrent hospitalizations

ACC, American College of Cardiology; AHA, American Heart Association

Patient-reported symptoms

The majority of patients with possible heart failure will present themselves initially in primary care,[43] therefore it is important for a GP or PN to be able to identify symptoms predictive of this condition. Previous research has shown that the value of symptoms is limited in the diagnosis of heart failure.[44] Especially in early stages of heart failure, milder symptoms do occur which are generally insensitive for the diagnosis of heart failure.[41]

Frequently reported symptoms of heart failure are edema, dyspnea, and fatigue.[45] These symptoms have also been found in primary care studies in patients with heart failure.[42,43] Prior findings have shown that symptoms such as fatigue and breathlessness in patients with heart failure are associated with adverse outcomes.[46] However, most studies evaluating the value of symptoms in the diagnosis of heart failure have focused on populations treated in hospitals.[47] Furthermore, the majority of studies evaluated symptoms only in association with left ventricular systolic dysfunction and did not evaluate the association of symptoms with other cardiac abnormalities associated with heart failure such as diastolic dysfunction.[47] Information on heart failure symptoms in primary care hypertension patients could help in clinical practice to make a selection of patients who should be referred for further examination.

Psychological distress in hypertension patients

The 2012 European guidelines on cardiovascular disease prevention in clinical practice of the ESC and other societies on cardiovascular disease prevention state that psychological factors, such as depression, anxiety, and Type D personality (the tendency to experience negative emotions in combination with the tendency to inhibit the expression of emotions[48]), may contribute to the risk of developing CVD and may have impact on prognosis in patients with established disease.[49] This statement is supported by previous research that has shown an association between psychological distress such as depression,[50,51] anxiety,[52] and Type D personality,[53] and the incidence and/or prognosis of cardiac diseases such as CHD and heart failure. Furthermore, a systematic review showed an increased incidence of hypertension in participants with elevated symptoms of depression.[54] However, the Dutch guideline on CVRM does not explicitly include attention to psychological distress in their recommendations, although it is stated that especially work-related stress might be an important factor that might increase cardiovascular risk.[20]

Focus on psychological distress, such as depression or anxiety, in hypertension patients is relevant because psychological distress could be a possible barrier for adequate adherence to medication.[55] In general, adherence is seen as an important aspect of hypertension treatment, with non-adherence as one of the possible causes of resistant hypertension.[8] Prior findings have shown an independent association between poor medication adherence in elderly patients with hypertension and depression and/or anxiety.[55] However, other studies reported mixed or inconclusive results,[56] or found no relation between the level of blood pressure and psychological distress.[57] Most studies investigating a possible relation between psychological distress and CVD focused on out-patient clinic or hospital patients. Data of primary care populations are scarce. Therefore, more information is needed on the association between psychological distress and hypertension in primary care to be able to

conclude whether a focus on psychological distress in CVRM of hypertension patients is required.

There is an ongoing debate whether beta-blockers may be associated with (symptoms of) depression.[58] Lipophilic beta-blockers, such as metoprolol, can pass the blood-brain barrier and are most likely associated with adverse effects related to the central nervous system such as depression and fatigue.[59] Beta-blockers are still prescribed frequently in primary care hypertension patients, although the current CVRM guideline advises other antihypertensive medication as first choice treatment.[20] Evidence for an association between beta-blocker use and depression is inconclusive. Many studies, as described in a review on the association between beta-blockers and depression, were subject to methodological shortcomings that might explain the mixed results.[58] Also some recent studies with good methodological quality showed mixed findings.[60-63] However, these studies were mainly conducted in patients in whom beta-blockers are strongly recommended (e.g. patients with a prior MI[63], or patients with an implantable cardioverter defibrillator[61]), while currently no studies have examined the association between beta-blocker and depression in primary care hypertension patients.

Aims and outline of the thesis

This thesis presents the results of a study evaluating several aspects associated with CVRM in primary care hypertension patients aged between 60 and 85 years. The general aim of this thesis is to gain more insight into the clinical and psychological aspects associated with CVRM in elderly hypertension patients in primary care.

Hypertension management is an important part of CVRM as described in the Dutch guideline on CVRM. However, more information on the association between adherence to the guideline in relation to cardiovascular abnormalities diagnosed with echocardiography could be of great value. Therefore, *chapter 2* describes treatment of uncomplicated hypertension in primary care according to the Dutch guideline on CVRM and the association with abnormalities on an echocardiogram.

Little is known about cardiac dysfunction in unselected elderly patients with hypertension. Therefore, in *chapter 3* the prevalence of cardiac abnormalities assessed by echocardiography is described. Furthermore, in that chapter the association between SBP and cardiac abnormalities is evaluated.

Hypertension is an important risk factor for heart failure,[64] and most patients with possible heart failure will present themselves initially in primary care.[43] The prevalence of symptoms such as shortness of breath, fatigue, and edema in unselected elderly hypertension patients

is unknown, as well as the value of symptoms in the diagnosis of cardiac abnormalities assessed with echocardiography. In *chapter 4* the prevalence of heart failure symptoms is described, as well as the value of these symptoms in association with an abnormal echocardiogram in elderly primary care hypertension patients.

Until recently, the majority of research on the relation between psychological distress and cardiovascular risk has focused on patients being treated in hospital or outpatient-clinics. Previous findings on the association between psychological distress and hypertension are mixed. The objective of *chapter 5* was therefore to describe the prevalence of depression, anxiety, and Type D personality in primary care hypertension patients, and to study the association between psychological distress and SBP taking into account several confounders.

Although the prescription of beta-blockers for uncomplicated hypertension is no longer recommended in the current guidelines, they are still frequently prescribed in primary care hypertension patients.[20] Previous research has shown mixed findings on the possible association between beta-blocker use and depression, although these studies often had methodological shortcomings. *Chapter 6* describes the association of lipophilic beta-blockers with depression in primary care hypertension patients.

Finally, in *chapter 7* the main findings of this thesis are summarized and strengths and limitations, clinical implications of the findings, and directions for future research are discussed.

Research design

The data reported on in this thesis were collected as part of the CHELLO (Casefinding Hartfalen EersteLijns Longitudinaal Onderzoek) study. CHELLO is a study on the screening of elderly primary care hypertension patients for cardiac abnormalities. Between June 2010 and January 2013, five different GP practices affiliated with the primary care organization PoZoB participated in this study. During this period, the CVRM program started within PoZoB and the sample selected for the CHELLO study was embedded within this program.

Inclusion criteria

Patients between 60 and 85 years of age with diagnosed hypertension according to the International Classification of Primary Care (ICPC) code K86 (primary hypertension without organ damage) and/or ICPC K87 (primary hypertension with organ damage) in their medical record were considered eligible for study participation.

Exclusion criteria

Patients were excluded in case of a previous diagnosis of heart failure and/or treatment by a cardiologist at the time of inclusion (patients with previous CHD, not being seen by a cardiologist were eligible for study participation); a history of severe psychiatric illness other than mood or anxiety disorders; cognitive impairments (e.g. dementia) determined by the GP; terminal cancer; insufficient knowledge of the Dutch language or inability to read.

Table 2. Content of the interview, baseline variables, and examination

Variables	***Source***
Demographics	
Age	Purpose designed questions
Gender	Purpose designed questions
Marital status	Purpose designed questions
Education level	Purpose designed questions
Employment status	Purpose designed questions
Clinical variables and risk factors	
Symptoms of heart failure	Standardized questionnaire
Height	Measurement
Weight	Measurement
Systolic and diastolic blood pressure	Measurement (after 20 and 40 minutes of resting)
Current smoking	Purpose designed questions
Alcohol consumption	Purpose designed questions
Comorbidities	
Previous MI	Review of medical record
Peripheral arterial disease	Review of medical record
Previous CVA / TIA	Review of medical record
Asthma or COPD	Review of medical record
Type 2 diabetes	Review of medical record
Use of medication	Review of medical record
Beta-blockers	
ACE-inhibitors	
ARBs	
Calcium antagonists	
Diuretics	
Psychological variables	
Depression (PHQ-9)	Validated questionnaire
Anxiety (GAD-7)	Validated questionnaire
Type D personality (DS14)	Validated questionnaire

MI, myocardial infarction; CVA, cerebrovascular accident; TIA, transient ischemic attack; ACE, angiotensin converting enzyme; ARB, angiotensin receptor blocker; PHQ-9,9-item Patient Health Questionnaire; GAD-7, 7-item Generalized Anxiety Disorder; DS, Distressed Scale

Study procedure and data collection

Eligible patients (n=913) received information about the study both orally and in writing, and were asked to sign an informed consent that was sent by postal mail. Within three weeks patients were contacted by phone, and in case of informed consent an appointment for an interview at the local GP office was scheduled. During this first appointment, eligible patients underwent a structured interview (Table 2).

Assessment of cardiac function with electrocardiography and echocardiography

The electrocardiogram (ECG) and echocardiogram were carried out by a trained and experienced echocardiographist of the local Primary Care Laboratory of the city of Eindhoven, "Diagnostiek voor U". All the electrocardiograms and echocardiograms were reviewed by a cardiologist specialized in echocardiography.

A standard resting 12-lead ECG was recorded. ECG characteristics and abnormalities studied included heart rate, arrhythmias (atrial fibrillation), conduction abnormalities (left bundle branch block, left fascicular block, atrio-ventricular conduction), left and right ventricular hypertrophy, ischemic heart disease, and (prior) myocardial infarction.

Echocardiograms were made with the Philips CX 50 equipped with a cardiology package and an s5 transducer. The echocardiogram was classified as abnormal according to the criteria as shown in Table 3. Furthermore, ten echocardiograms (randomly selected) were performed together with a cardiologist who observed whether the echocardiographist accurately followed the prescribed protocol.

Table 3. Categories of cardiac abnormalities on the echocardiogram

Category	*Cut-off*
LVEF	<55%[65]
LVH	Septal and posterior wall thickness of ≥ 13 mm (moderate or severe[65])
LAVI	>29 ml/m² [65]
Diastolic dysfunction	E/A ratio of <1 and deceleration times of >200ms, and presence of LVH in case of grade I diastolic dysfunction[66]
RVH	Subcostal wall thickness of ≥6mm (mild, moderate or severe)
Aortic valve insufficiency	Moderate or severe abnormalities, AI P1/2 time
Aortic valve stenosis	Mean gradient ≥ 30 mmHg
Mitral valve insufficiency	Moderate or severe abnormalities, grade 2 or higher
MAC	Presence of MAC
Tricuspid valve insufficiency	Moderate or severe abnormalities, grade 2 or higher
Wall motion abnormalities	Hypokinesia, akinesia and dyskinesia
Aortic dilatation	Moderate or severe abnormalities, >40mm
Cardiomyopathy	Hypertrophic cardiomyopathy
Congenital abnormalities	Atrial septal defect, bicuspid aortic valve

LVEF, left ventricular ejection fraction; LVH, left ventricle hypertrophy; LAVI, left atrium volume index; MAC, mitral annulus calcification; RVH, right ventricle hypertrophy.

An adapted protocol was used to assess cardiac abnormalities on the echocardiogram suitable for use in general practice. The Simpson formula was used to calculate left ventricular ejection fraction (LVEF) in the apical four-chamber and apical two-chamber view.[65] LVH was calculated with measurement of septal and posterial wall thickness and left atrial volume index (LAVI) was calculated with left atrial volume/body surface area (ml/m^2).[65] In individuals aged >60 years without a history of CVD, an E/A ratio of <1 and DTs of >200ms are common, therefore, diastolic dysfunction was considered when also LVH was present in case of grade I diastolic dysfunction.[66] Right ventricle hypertrophy was calculated with measurement of right ventricle subcostal wall thickness.[67] Aortic valve insufficiency, aortic valve stenosis, mitral valve insufficiency, mitral valve stenosis, mitral annulus calcification (MAC), tricuspid valve insufficiency, wall motion abnormalities, aortic dilatation, cardiomyopathy, and congenital abnormalities were assessed (Table 3). The GP of the patient received the results of the echocardiogram and in case of a clinically relevant abnormal echocardiogram, the cardiologist advised the GP. The three different categories of advice were: 1) (immediate) referral to a cardiologist, 2) advice to repeat the echocardiogram within 1 to 5 years, and 3) advice to change the medication regimen.

Psychological measures

The 14-item Type D Scale (DS14) was used to assess Type D personality, 7 items of this questionnaire assess negative affectivity (NA) and 7 items assess social inhibition (SI). Items are rated on a 5-point Likert scale (range 0-56). Previous research showed that the DS14 is a valid and reliable instrument to assess Type D personality.[68] Both NA and SI scales can be used as continuous scales, and also to classify patients as 'Type D' versus 'non-Type D'. A cut-off of ≥10 on both subscales was found to be optimal according to Item Response Theory.[69]

The 9-item Patient Health Questionnaire (PHQ-9) was used to assess symptoms of depression. Items are rated on a 4-point Likert scale (range 0-27).[70] In this study, a cut off of ≥9 was used which is suitable for elderly individuals in primary care, with a sensitivity of 88% and specificity of 80% and an area under the curve for the detection of a major depressive disorder of .87.[71]

Symptoms of anxiety were measured with the Generalized Anxiety Disorder-7 (GAD-7) scale. The seven items are rated on a 4-point Likert scale (range 0-21), and increasing scores are associated with functional impairment and disability.[72] In this study, a cut-off of ≥8 was used since this has a high sensitivity (92%) and specificity (76%) for the detection of generalized anxiety disorder, as well as for the detection of any anxiety disorder (respectively 77% and 82%).[73] The GAD-7 has an area under the curve of .91 for detecting generalized anxiety disorder.[73]

Both the PHQ-9 and the GAD-7 are derived from the Primary Care Evaluation of Mental Disorders (PRIME-MD), which was originally designed for the diagnosis of five mental disorders (including depression and anxiety) in primary care by using DSM IV criteria.[74,75]

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Chapter 2

Behandeling van Hypertensie bij Oudere Patiënten in de Huisartsenpraktijk Volgens de Huidige CVRM Richtlijn

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Submitted

Abstract

Objective: To determine adherence to the Dutch guideline on cardiovascular risk management (CVRM) and the association between adherence to the guideline and cardiac dysfunction as established with echocardiography in elderly primary care patients with hypertension.

Design: Cross-sectional study in five general practices in the South-East of the Netherlands affiliated with the primary care organization PoZoB and participating in a CVRM program.

Method: Between June 2010 and January 2013, primary care hypertension patients aged between 60 and 85 years were included if they did not have known heart failure or were treated by a cardiologist. A total of 568 patients with no history of myocardial infarction and/or atrial fibrillation were included and underwent an echocardiogram.

Results: Of the 568 patients included in this study, 214 (38%) were not treated according to the guideline. In these patients, abnormalities on the echocardiogram were observed in 37% versus 21% of patients who were treated according to the guideline ($p<.001$). Logistic regression analysis showed a significant and clinically relevant association between an abnormal echocardiogram and treatment not conform to the guideline in the unadjusted (OR=2.18, 95% CI: 1.50-3.18) and adjusted analyses (OR=2.13, 95% CI:1.54-3.47).

Conclusion: Primary care hypertension patients who were not treated according to the Dutch CVRM guideline had significantly more often an abnormal echocardiogram. Future research should focus on the consequences of (non)adherence to hypertension treatment guidelines and a possible integration of an echocardiogram in the routine program of CVRM.

Samenvatting

Doel: Het vaststellen van de mate waarin de NHG/CBO richtlijn cardiovasculair risicomanagement (CVRM) wordt gevolgd en de samenhang tussen het volgen van de richtlijn en hartafwijkingen vastgesteld met een echocardiogram bij oudere hypertensiepatiënten in de huisartsenpraktijk.

Opzet: Cross-sectioneel onderzoek in vijf huisartsenpraktijken in Zuidoost-Brabant die binnen de zorggroep PoZoB betrokken zijn bij CVRM.

Methode: Tussen juni 2010 en januari 2013 werden eerstelijns hypertensiepatiënten, tussen 60 en 85 jaar oud, zonder diagnose hartfalen en niet onder behandeling bij een cardioloog benaderd voor het onderzoek. In totaal werden 568 patiënten, zonder bekend hartinfarct in de voorgeschiedenis en/of atrium fibrilleren geïncludeerd waarbij een echocardiogram werd afgenomen

Resultaten: Van de 568 geïncludeerde patiënten werden 214 (38%) niet volgens de richtlijn behandeld. In deze groep werd bij 37% afwijkingen op het echocardiogram gevonden versus 21% in de groep die wel volgens de richtlijn werd behandeld ($p < .001$). Logistische regressie liet een significante en klinisch relevante samenhang zien tussen behandeling niet volgens de richtlijn en afwijkingen op het echocardiogram in de ongecorrigeerde (OR=2.18, 95% CI: 1.50-3.18) en in gecorrigeerde analyses (OR=2.13, 95% CI:1.54-3.47).

Conclusie: Eerstelijns hypertensiepatiënten die niet volgens de richtlijn CVRM behandeld werden hadden significant vaker afwijkingen op het echocardiogram. Toekomstig onderzoek zou zich kunnen richten op de consequenties van het wel/niet volgen van hypertensie richtlijn en een mogelijke integratie van het echocardiogram in het zorgprogramma CVRM.

Inleiding

De Framingham studie heeft laten zien dat volwassenen van 55 jaar oud 90% kans hebben om hypertensie te ontwikkelen in hun leven.[1] In Nederland loopt de prevalentie van hypertensie bij mannen en vrouwen op van respectievelijk 61% en 55% in de leeftijdscategorie 60-70 jaar, tot ongeveer 70% bij beiden tussen 70-80 jaar.[2] Hypertensie is niet alleen een belangrijke risicofactor voor het krijgen van een transient ischemic attack (TIA)/cerebrovasculair accident (CVA),[3] maar ook voor verschillende hartafwijkingen die bijdragen aan de ontwikkeling van hartfalen.[4] Behandeling van de bloeddruk leidt tot een daling van de incidentie van CVA's, coronaire events en hartfalen.[5]

Sinds 2006 bestaat de multidisciplinaire richtlijn cardiovasculair risicomanagement (CVRM) van het Kwaliteitsinstituut voor de Gezondheidszorg (CBO) en het Nederlandse Huisartsen Genootschap (NHG) waarin de behandeling van hypertensie een belangrijk onderdeel is. In 2011 is er een herziene versie verschenen, met daarin wijzigingen in het advies voor het voorschrijven van antihypertensiva. De richtlijn adviseert bij patiënten met hypertensie, met verhoogd cardiovasculair risico, een behandeling met antihypertensiva met als doel een systolische bloeddruk (SBD) onder de streefwaarde (SBD≤140 mmHg bij patiënten tot 80 jaar, SBD≤160 bij patiënten van 80 jaar en ouder, SBD≤130 mmHg bij patiënten met diabetes).[6] Het bereiken van de streefwaarde bij patiënten met hypertensie is niet eenvoudig. Verschillende Europese studies rapporteerden een SBD onder de streefwaarde bij slechts 23% tot 38% van de patiënten.[7,8] Een onderzoek in Nederland onder de algemene populatie in 2007 liet zien dat bij 42% van de deelnemende hypertensie patiënten de bloeddruk voldoende onder controle was.[9]

De huidige richtlijn adviseert te starten met een diureticum of een calciumantagonist, vervolgens kan een ACE-remmer of een angiotensinereceptorantagonist (ARB) worden toegevoegd. Ten slotte kan een diureticum worden gecombineerd met een calciumantagonist en ACE-remmer of ARB. In tegenstelling tot de vorige richtlijn, is er voor bètablokkers in de huidige richtlijn een bescheiden rol weggelegd en worden deze alleen geadviseerd bij het bestaan van cardiale aandoeningen, zoals een eerder doorgemaakt hartinfarct of ritmestoornissen.[6] Tot op heden ontbreken in de Nederlandse populatie cijfers over de mate waarin deze richtlijn voor behandeling van hypertensie in de eerste lijn wordt gevolgd.

Hypertensie is een belangrijke risicofactor voor het ontwikkelen van hartfalen. Echocardiografie wordt gezien als de gouden standaard voor het vaststellen van hartafwijkingen in relatie tot hartfalen.[10,11] Een afwijkend echocardiogram bij hypertensiepatiënten boven 60 jaar is niet hetzelfde als hartfalen. Maar veel echocardiografische afwijkingen bij deze patiënten (zoals ventrikel hypertrofie, diastolische dysfunctie, verminderde ejectiefractie, kleplijden) zijn

belangrijke risicofactoren voor het ontwikkelen van hartfalen.[4]

In 2010 is de eerstelijns zorggroep PoZoB in Zuidoost Brabant van start gegaan met de implementatie van het zorgprogramma CVRM, waarvan de behandeling van hypertensie een belangrijk onderdeel uitmaakt. Inmiddels zijn er ongeveer 25.000 hypertensie patiënten in dit zorgprogramma geïncludeerd. De vraagstellingen van de huidige studie waren om te onderzoeken (1) in welke mate de richtlijn CVRM wordt gevolgd bij de behandeling van hypertensie in de eerste lijn en (2) de mogelijke relatie tussen het bestaan van klinisch relevante afwijkingen op het echocardiogram en het wel/niet behandeld worden volgens de richtlijn CVRM.

Patiënten en methode

Tussen juni 2010 en januari 2013 werden in vijf verschillende huisartspraktijken patiënten tussen 60 en 85 jaar met een 'International Classification of Primary Care' code voor hypertensie (K86/K87) in hun medisch dossier benaderd voor dit cross-sectionele onderzoek. De volgende patiënten werden geëxcludeerd: reeds onder behandeling bij een cardioloog, ernstige psychiatrische problematiek (psychose, borderline), cognitieve beperkingen, terminale ziekte, onvoldoende kennis van de Nederlandse taal.

De studie werd goedgekeurd door de medische ethische toetsingscommissie van het St.- Elisabeth ziekenhuis in Tilburg.

Procedure

Na het ontvangen van de informed consent werd een afspraak ingepland voor een interview in de eigen huisartsenpraktijk. Tijdens dit interview door een verpleegkundige of praktijkondersteuner werden gewicht en lengte gemeten en een aantal gevalideerde en gestandaardiseerde vragenlijsten afgenomen. Daarnaast werd de bloeddruk gemeten na ongeveer 20 en 40 minuten in zittende houding. De gemiddelde waarden van beide bloeddrukken werden gebruikt om de SBD waarde vast te stellen. Bij alle patiënten werd tijdens een tweede afspraak een elektrocardiogram (ECG) en echocardiogram gemaakt in de eigen huisartsenpraktijk door een gespecialiseerde echocardiografist van het huisartsenlaboratorium in Eindhoven, 'Diagnostiek voor U' en beoordeeld door een cardioloog gespecialiseerd in echocardiografie. Er was sprake van een afwijkend echocardiogram (op basis van een protocol aangepast voor de eerstelijn, gebaseerd op de richtlijnen voor echocardiografie[12,13]) bij een verminderde linkerkamer ejectiefractie (<55%), linker ventrikel hypertrofie (matig/ernstig), vergroot linker atrium (linker atrium volume index>29 ml/m^2), diastolische dysfunctie, en (voor de leeftijd) klinisch relevant kleplijden.

Klinische variabelen verkregen uit het medisch dossier waren een eerder doorgemaakt hartinfarct, bestaan van perifeer vaatlijden, eerder doorgemaakt CVA of TIA, bestaan van chronisch obstructief longlijden (COPD)/astma, bestaan van diabetes type 2, het aantal jaren sinds de diagnose hypertensie en het medicatiegebruik.

Statistische analyse

De statistische analyses werden uitgevoerd met behulp van het *IBM Statistical Package for the Social Sciences* versie 19.0. De kenmerken van de steekproef werden gestratificeerd naar wel/geen behandeling volgens de richtlijn. Verschillen tussen groepen op continue variabelen werden bekeken met behulp van Student's t-toetsen, zo nodig werden Welch's t-toetsen gebruikt. Bij het toetsen van verschillen tussen groepen op nominale variabelen werden Chi^2 toetsen gebruikt. De associatie tussen behandeling wel/niet volgens de richtlijn en het hebben van afwijkingen op het echocardiogram werd getoetst met multiple logistische regressie analyse (Odds ratio [OR], 95% betrouwbaarheidsinterval [BI]) gecorrigeerd voor de confounders leeftijd, geslacht, opleiding, roken, alcohol consumptie, BMI, het bestaan van diabetes type 2, het aantal jaren sinds de diagnose hypertensie en SBD.

Resultaten

Van de 913 patiënten die benaderd werden voor deelname deden uiteindelijk 619 (68%) patiënten mee. Vervolgens werden er post-hoc 2 patiënten geëxcludeerd omdat zij bij een cardioloog onder behandeling waren op het moment van inclusie. Van 5 patiënten was er geen informatie beschikbaar over de bloeddruk, van 6 patiënten waren er geen gegevens over medicatiegebruik, ook zij werden geëxcludeerd. Het voorschrijfbeleid voor hypertensie is anders in geval een eerder hartinfarct en/of atriumfibrilleren, daarom werden 38 patiënten met een hartinfarct in hun voorgeschiedenis en/of atriumfibrilleren op het ECG geëxcludeerd van de analyse. De kenmerken van de 568 overgebleven patiënten zijn weergegeven in tabel 1. In totaal werden 214 (38%) van de 568 patiënten niet behandeld volgens de richtlijn. Hiervan kregen 24 patiënten met langer dan één jaar de diagnose hypertensie (range=2-30 jaar, gemiddelde=11 jaar, SD=9.7) én een SBD boven de streefwaarde, geen medicatie. Binnen de totale groep (n=568) kregen van de patiënten met 1 antihypertensivum 33 patiënten een bètablokker, van de patiënten met 2 antihypertensiva kregen 68 patiënten een combinatie die niet in de richtlijn wordt geadviseerd (waarvan 61 een combinatie met een bètablokker), en van de patiënten met 3 of meer antihypertensiva kregen 84 patiënten een combinatie die niet in de richtlijn wordt geadviseerd (waarvan 77 een combinatie met een bètablokker).

Tabel 1. Kenmerken van de steekproef (n=568) gestratificeerd naar behandeling wel/niet volgens de CVRM richtlijn

Kenmerk	*Totale groep n=568*	*Behandeld volgens de huidige richtlijn (n=354, 62%)*	*Niet behandeld volgens de huidige richtlijn (n=214, 38%)*	*P-waarde*
Demografische gegevens				
Man	243 (43%)	150 (42%)	93 (44%)	.800
Leeftijd, gemiddelde (SD)	70 (6.5)	70 (6.4)	70 (6.7)	.499
Partner	430 (76%)	268 (76%)	162 (76%)	.999
Laag opgeleid[a]	71 (13%)	45 (13%)	26 (12%)	.844
Risicofactoren				
Roken	78 (14%)	49 (14%)	29 (14%)	.922
Alcohol consumptie ≥ 2 glazen per dag (gemiddeld)	176 (31%)	114 (32%)	62 (29%)	.420
BMI kg/m², gemiddelde (SD)	28 (4.3)	28 (4.4)	28 (4.1)	.562
SBD boven de streefwaarde[b]	378 (67%)	230 (65%)	148 (69%)	.305
Klinisch relevant afwijkend ECG (n=580)	81 (14%)	47 (13%)	34 (16%)	.388
Afwijkingen op het echocardiogram	**155 (27%)**	**75 (21%)**	**80 (37%)**	**<.001**
Medische voorgeschiedenis				
Aantal jaren sinds diagnose hypertensie, gemiddelde (SD)	**12 (11)**	**11 (10.3)**	**14 (11.6)**	**.002**
Perifeer vaatlijden	20 (4%)	11 (3%)	9 (4%)	.491
Eerder doorgemaakt TIA/CVA	47 (8%)	30 (9%)	17 (8%)	.824
Diabetes type 2	63 (11%)	38 (11%)	25 (12%)	.727

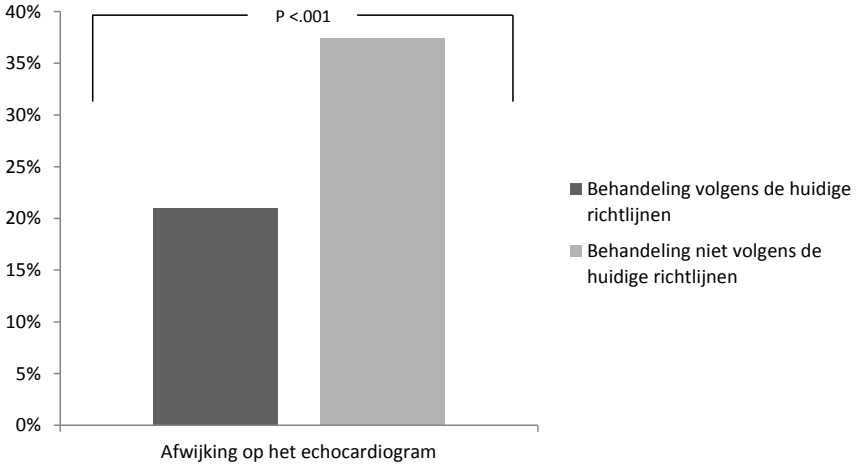
a. Laag opgeleid; minder dan middelbare school

b. Streefwaarde SBD ≤130 mmHg voor patiënten met diabetes type 2, ≤140 voor patiënten onder de 80 jaar, ≤160 voor patiënten van 80 jaar en ouder

BMI, body mass index; SBD, systolische bloeddruk; TIA, transient ischemic attack; CVA, cerebrovasculair accident; ECG, electrocardiogram

In totaal hadden 378 patiënten (67%) een SBD boven de streefwaarden zoals gedefinieerd in de CVRM richtlijn.[6] Tussen de groepen wel/niet behandeld volgens de richtlijn vonden we significante verschillen in afwijkingen op het echocardiogram (21% versus 37%, p<.001, figuur 1), en in het gemiddelde aantal jaren sinds de diagnose hypertensie (11 versus 14 jaar, p=.002, tabel 1). In de enkelvoudige logistische regressie was er een significante samenhang tussen afwijkingen op het echocardiogram en hogere leeftijd (OR=1.06, 95% BI:1.03-1.09), hogere SBD (OR=1.02, 95% BI:1.01-1.03) en behandeling niet volgens de richtlijn (OR=2.22, 95% BI:1.52-3.24). In de gecorrigeerde regressie analyse was er een onafhankelijke en significante samenhang tussen een afwijkend echocardiogram en behandeling niet volgens de richtlijn (OR=2.31, 95% BI:1.54-3.47), evenals met hogere leeftijd (OR=1.05, 95% BI:1.02-1.09) en hogere SBD (OR=1.02, 95% BI:1.01-1.03, tabel 2).

Figuur 1. Behandeling wel/niet volgens de huidige CVRM richtlijn opgesplitst naar wel/geen afwijkingen op het echocardiogram bij 568 patiënten met hypertensie tussen 60-85 jaar die behandeld worden in de eerstelijn. (Pearson Chi2=17.6, df =1, p<.001).



Afwijkingen; linker ventrikel ejectie fractie<55%, linker ventrikel hypertrofie, diastolische dysfunctie, vergroot linker atrium, wandbewegingsstoornissen, aorta-, mitralis-, of tricuspidalisklepafwijkingen, rechter ventrikel hypertrofie

Tabel 2. (On-)gecorrigeerde odds ratio's voor de associatie tussen behandeling niet volgens de richtlijn (onafhankelijke variabele) en afwijkingen op het echocardiogram (afhankelijke variabele) bij 568 patiënten met hypertensie tussen 60-85 jaar die behandeld worden in de eerstelijn.

Ongecorrigeerde odds ratio's	*OR*	*95% Betrouwbaarheidsinterval*
Leeftijd	**1.06**	**1.03-1.09**
Geslacht (vrouw)	1.05	.72-1.52
Laag opgeleid[a]	.89	.51-1.58
Roken	.60	.33-1.08
Alcohol consumptie ≥ 2 glazen per dag	.84	.56-1.27
BMI	.97	.93-1.02
Bestaan van diabetes type 2	1.07	.60-1.92
Aantal jaren sinds diagnose hypertensie	1.00	.98-1.02
SBD in mmHg	**1.02**	**1.01-1.03**
Behandeling niet volgens de huidige richtlijn	**2.18**	**1.50-3.18**
Gecorrigeerde odds ratio's		
Leeftijd	**1.05**	**1.02-1.09**
Geslacht (vrouw)	1.16	.76-1.77
Laag opgeleid	.67	.35-1.28
Roken	.57	.30-1.10
Alcohol consumptie ≥ 2 glazen per dag	.80	.50-1.26
BMI	.96	.91-1.01
Bestaan van diabetes type 2	1.17	.63-2.19
Aantal jaren sinds diagnose hypertensie	.99	.97-1.00
SBD in mmHg	**1.02**	**1.01-1.03**
Behandeling niet volgens de huidige richtlijn	**2.31**	**1.54-3.47**

a. Laag opgeleid, minder dan middelbare school
BMI, body mass index; SBD, systolische bloeddruk

Discussie

De resultaten van dit onderzoek laten zien dat 38% van een steekproef van 568 hypertensiepatiënten uit het zorgprogramma CVRM van PoZoB niet wordt behandeld volgens de huidige richtlijn CVRM. Deze 38% bestaat grotendeels uit patiënten die een bètablokker krijgen voorgeschreven al dan niet in combinatie met een ander antihypertensivum (n=171), zonder dat er sprake is van een hartinfarct in de voorgeschiedenis of hartfalen. Daarnaast is er een kleine groep patiënten die geen antihypertensiva krijgt voorgeschreven maar wel een SBD hebben boven de streefwaarde (n=29). De patiënten die niet volgens de richtlijn CVRM worden behandeld hebben vaker afwijkingen op een echocardiogram dan de patiënten die wel volgens de richtlijn behandeld worden (37% vs. 21%, p<.001). Deze samenhang blijft significant na correctie voor confounders zoals leeftijd, jaren sinds diagnose van hypertensie, en de hoogte van de SBD.

Ondanks de aanwezigheid van richtlijnen en het bestaan van een groot aantal antihypertensiva is de praktijk vaak weerbarstig. Niet alleen werd de richtlijn bij 38% niet gevolgd, een SBD onder de streefwaarde werd slechts bij 33% van de patiënten gemeten. Dit komt overeen met resultaten uit andere Europese studies, waar bij maximaal 38% van de hypertensiepatiënten een bloeddruk onder de streefwaarde werd gevonden.[7,8] Een terughoudend voorschrijfbeleid door huisartsen is een mogelijke oorzaak voor deze lage cijfers; zo is bij ouderen het gebruik van antihypertensiva een bekende oorzaak van vallen door orthostatische hypotensie.[14] Patiënten die niet volgens de richtlijn behandeld werden hadden echter wel vaker afwijkingen op het echocardiogram. Bij 24 patiënten die geen antihypertensiva kregen voorgeschreven was de gemiddelde duur sinds de diagnose hypertensie maar liefst 11 jaar. Men kan zich afvragen of zoveel jaar na het stellen van de diagnose hypertensie een afwachtend beleid nog is te verdedigen, zeker gelet op de leeftijd (gemiddeld 70 jaar). Daarnaast kreeg het overgrote gedeelte van de patiënten die niet volgens de richtlijn behandeld werden een (combinatie met een) bètablokker voorgeschreven. Uit eerder onderzoek blijkt dat het gebruik van bètablokkers als monotherapie of eerste keus antihypertensivum minder effectief is in het verminderen van cardiovasculair risico (waaronder de incidentie van een beroerte en cardiovasculaire sterfte).[15] Bovendien is de therapietrouw bij het gebruik van bètablokkers lager omdat deze meer bijwerkingen geven.[15] Het feit dat bijna 40% van de patiënten niet volgens de richtlijn werd behandeld moet bezien worden in het licht van een inclusie van ongeveer 25% van de deelnemers voordat de herziene richtlijn CVRM werd uitgebracht. Dit kan echter slechts gedeeltelijk het niet opvolgen van de nieuwe richtlijn verklaren.

Een klinisch relevant afwijkend echocardiogram is niet hetzelfde als het hebben van hartfalen. Echter, de literatuur is zeer eenduidig als het gaat om de voorspellende waarde

van een afwijkend echocardiogram op het ontwikkelen later van hartfalen.[16-20] Op basis van het afwijkend echocardiogram werden door een onafhankelijk cardioloog (van buiten de regio) adviezen gegeven aan de huisarts. Deze bestonden bij 50% van de afwijkingen uit een eenvoudig medicatieadvies (voornamelijk ophogen van de gebruikte dosis, of toevoegen van een ACE-remmer of ARB aan bestaande medicatie).

Dit onderzoek kent een aantal beperkingen. Allereerst is dit een cross-sectioneel onderzoek, waardoor het doen van causale uitspraken niet mogelijk is. Prospectief onderzoek moet aantonen of het volgen van de richtlijn CVRM ook effect heeft op harde eindpunten zoals cerebrovasculaire events, cardiovasculaire ziekte (ontwikkelen van hartfalen) en sterfte. Omdat de huidige studie plaatsvond binnen het CVRM zorgprogramma van PoZoB - hetgeen in analogie met het eerstelijns diabetes programma in principe ''levenslange'' follow-up impliceert - is het eenvoudig om over 5 jaar bij de participanten (al dan niet selectief) het echocardiogram te herhalen. Op deze manier is voor een eerstelijns hypertensie populatie de voorspellende waarde van een afwijkend echocardiogram op het ontwikkelen van klinisch relevant hartfalen eenvoudig te bepalen.

Het zou mogelijk kunnen zijn dat een geselecteerde groep participeerde in het onderzoek, maar er was een hoge respons voor participatie in deze studie (68%). Bovendien bleek de man/vrouw verdeling opgesplitst naar leeftijdscategorieën goed overeen te komen met de totale hypertensie CVRM populatie van PoZoB. Dit suggereert dat de cijfers van de huidige steekproef representatief zijn voor de gehele hypertensie populatie in de leeftijd tussen 60 en 85 jaar binnen het CVRM programma van PoZoB. Indien bij 1/3 een afwijkend echocardiogram zou worden gevonden waarbij bij 50% een eenvoudig medicatie advies volstaat zou het toevoegen van een echocardiogram aan het CVRM protocol mogelijk te overwegen zijn. Het echocardiogram is goedkoop (75 euro), kan door huisartsen worden aangevraagd en in principe in de huisartsenpraktijk plaatsvinden. Toekomstig onderzoek in de eerstelijn zal de kosteneffectiviteit van het standaard invoeren van een periodiek uit te voeren echocardiogram bij hypertensie patiënten boven de 60 jaar in kaart moeten brengen.

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Chapter 3

Unexpected High Numbers of Abnormal Echocardiograms in Unselected Elderly Hypertension Patients in Primary Care

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Submitted

Abstract

Background: Hypertension is very prevalent and an important risk factor for heart failure. This study aimed to determine the prevalence of cardiac abnormalities on an echocardiogram, in association with systolic blood pressure >160 mmHg, and relevance of screening in elderly primary care hypertension patients.

Methods: 596 primary care hypertension patients aged between 60-85 years, without known heart failure, not currently treated by a cardiologist, were included in this cross-sectional study and underwent an echocardiogram and structured interview including blood pressure assessment between June 2010 and January 2013**.**

Results: An abnormal echocardiogram was found in 30% (n=181) including: dilated left atrium (>29ml/m²) in 10% (n=62); reduced left ventricle ejection fraction (<55%) in 9% (n=51); left ventricle hypertrophy in 6% (n=38); and diastolic dysfunction in 6% (n=36) of the patients. These 4 categories included 133/181 abnormal echocardiograms. The remaining 48 patients had miscellaneous conditions. 38% of the patients had a systolic blood pressure of 140-160 mmHg, and 29% had a systolic blood pressure of >160 mmHg. After adjustment for other risk factors, a systolic blood pressure of >160 mmHg (apart from age, OR:1.07, 95% CI:1.03-1.10) was independently related to an abnormal echocardiogram (OR:1.57, 95% CI:1.03-2.38).

Conclusion: Screening of unselected primary care hypertension patients with an echocardiogram results in an unexpected high number (30%) of abnormal echocardiograms, prospective studies have shown these to be associated with poor cardiac outcomes. Furthermore 29% of patients had a systolic blood pressure of >160 mmHg. Screening of all elderly primary care hypertension patients should be considered.

Introduction

Hypertension is a highly prevalent condition, the Framingham study described a lifetime risk for developing hypertension of 90% in people with a normal blood pressure at age 55.[1] Hypertension can result in coronary artery disease and changes in ventricular function and structure, and is a major risk factor for developing heart failure.[2] Recent heart failure guidelines indicate that early diagnosis and treatment of heart failure are paramount for reducing morbidity and mortality.[3] The American guidelines for assessment of cardiovascular risk in asymptomatic adults suggest that echocardiography to detect left ventricle hypertrophy (LVH) should be considered in adults with hypertension.[4] In 2011, the American Heart Association (AHA) published a document on Hypertension in the Elderly in which they advocated to assess an echocardiogram in a sub-group of elderly.[2]

In primary care, treatment of hypertension as part of cardiovascular risk management has become a major issue. A primary care study in patient with hypertension showed that more severe hypertension is associated with a higher risk of cardiovascular events.[5] However, achieving optimal blood pressure control in hypertension patients is difficult,[6] with even poorer results with increasing age.[7] Symptomatic heart failure is generally preceded by asymptomatic cardiac dysfunction or changes in cardiac structure.[8] In a previous study in elderly hypertensive women, LVH was a main factor associated with unrecognized heart failure, especially in those with less than optimal blood pressure control.[9] Appropriate treatment with medication can prevent or delay the onset of symptoms of heart failure and also reduce mortality.[10] Also valvular heart disease and wall motion abnormalities can be major causes of heart failure and are related to coronary artery disease.[11] The current European guidelines for diagnosis and treatment of acute and chronic heart failure state that echocardiography is one of the most useful tests, which can be used to assess left and right ventricular systolic and diastolic function, wall motion, wall thickness, and valvular function.[3] Until now, no data are available on the prevalence of abnormal cardiac outcomes in primary care hypertension patients with no established cardiac disease. Although echocardiography is nowadays a cheap and non-invasive assessment with high sensitivity to detect cardiac abnormalities, it is not commonly used in primary care.[12]

In the present study, a sample of elderly primary care patients with hypertension was screened with the aid of echocardiography, using a protocol suitable for the assessment of cardiac abnormalities in a primary care setting. The objectives of the current study were to examine (1) the prevalence of an abnormal echocardiogram in elderly hypertension patients in primary care, (2) the number of patients with appropriately regulated blood pressure, and (3) the relation between the blood pressure and an abnormal echocardiogram, after adjustment for several confounders.

Methods

Study design and patient population

Between June 2010 and January 2013, primary care patients aged between 60-85 years with an International Classification of Primary Care for hypertension (K86/K87) in their medical record, were recruited from GPs affiliated with the primary care organization PoZoB.

Patients were excluded in case of a previous diagnosis of heart failure and/or treatment by a cardiologist at the time of inclusion (patients with a previous myocardial infarction, not being followed by a cardiologist were included in the study); severe psychiatric illness other than mood or anxiety disorders; serious cognitive impairments; terminal cancer; insufficient knowledge of the Dutch language, or inability to read. This study complies with the Declaration of Helsinki and was approved by the Medical Ethics Board of the st.-Elisabeth Hospital in Tilburg, the Netherlands.

Study procedure and data collection

Eligible patients received information about the study both orally and in writing. In case of informed consent, an appointment for an interview was scheduled. During this first appointment with a health care nurse at their local GP's office, eligible patients underwent a structured interview and physical examination. Blood pressure was measured after approximately 20 and 40 minutes of sitting. The mean value of both blood pressure measurements was used for data analysis. In addition, demographic and clinical variables were obtained during the interview and by reviewing the patient's medical records. After the interview, a second appointment was planned for an echocardiogram, also at the local GP office.

Assessment of the echocardiogram

The echocardiogram was carried out and evaluated by an experienced echocardiographist of the local Primary Care Laboratory "Diagnostiek voor U" in Eindhoven, The Netherlands. After assessment by the echocardiographist, all the echocardiograms were reviewed by a cardiologist specialized in echocardiography, who indicated if the echocardiogram was abnormal according to the criteria as shown in Table 1.

Echocardiograms were made with the Philips CX 50 equipped with a cardiology package and an s5 transducer. Because the echocardiogram was made in the local general practices, a simplified protocol was used to assess cardiac abnormalities. Left ventricular ejection fraction (LVEF) was calculated using the Simpson formula in the apical four-chamber and apical two-chamber view.[13] LVH was calculated with measurement of septal and posterial

wall thickness and LA volume index (LAVI) was calculated with LA volume/body surface area (ml/m^2).[13] Because in individuals aged >60 years without a history of cardiovascular disease an E/A ratio<1 and deceleration times of >200ms are common, diastolic dysfunction was considered when also LVH was present in case of grade I diastolic dysfunction.[14] Right ventricle hypertrophy (RVH) was calculated with measurement of right ventricle subcostal wall thickness.[15] Furthermore, aortic valve insufficiency, aortic valve stenosis, mitral valve insufficiency, mitral valve stenosis, mitral annulus calcification (MAC), tricuspid valve insufficiency, wall motion abnormalities, aortic dilatation, cardiomyopathy, and congenital abnormalities were assessed. The cut off points for abnormal findings in the abovementioned categories are described in Table 1.

Table 1. Prevalence of abnormal echocardiogram parameters in 596 elderly primary care hypertension patients

Echocardiogram abnormality	*Total (n=596)*	*Men (n=264)*	*Women (n=332)*	*p-value*
LVEF<55%[13]	**51 (9%)**	**30 (11%)**	**21 (6%)**	**.029**
LVH; septal and posterior wall thickness≥13 mm (moderate/severe[13])	**38 (6%)**	**23 (9%)**	**15 (5%)**	**.037**
LAVI>29 ml/m^2 [13]	**62 (10%)**	**20 (8%)**	**42 (13%)**	**.044**
Diastolic dysfunction (E/A ratio<1 and DTs>200ms, and presence of LVH in case of grade I diastolic dysfunction)[14]	36 (6%)	14 (5%)	22 (7%)	.501
RVH; subcostal wall thickness≥6mm (mild/moderate/severe)	16 (3%)	7 (3%)	9 (3%)	.964
Aortic valve insufficiency (moderate/severe, AI P1/2 time)	10 (2%)	3 (1%)	7 (2%)	.359
Aortic valve stenosis (mean gradient≥30 mmHg)	6 (1%)	5 (2%)	1 (0.3%)	n.a.
Mitral valve insufficiency (moderate/severe, ≥grade 2)	20 (3%)	6 (2%)	14 (4%)	.190
MAC	11 (2%)	6 (2%)	5 (2%)	.490
Tricuspid valve insufficiency (moderate/severe, ≥grade 2)	5 (1%)	0	5 (2%)	n.a.
Wall motion abnormalities (hypokinesia, akinesia or dyskinesia)	**26 (4%)**	**23 (9%)**	**3 (1%)**	**<.001**
Aortic dilatation>40mm (moderate/severe)	4 (1%)	2 (0.8%)	2 (0.6%)	n.a.
Cardiomyopathy (hypertrophic)	3 (0.5%)	1 (0.4%)	2 (0.6%)	n.a.
Congenital abnormalities	2 (0.3%)	1 (0.4%)	1 (0.3%)	n.a.
Total ≥1 abnormality	181 (30%)	84 (32%)	97 (29%)	.493

LAVI, left atrium volume index; LVEF, left ventricular ejection fraction; LVH, left ventricle hypertrophy; MAC, mitral annulus calcification; RVH, right ventricle hypertrophy.

Statistical analyses

Statistical analyses were performed using the IBM Statistical Package for the Social Sciences version 18.0. Differences between men and women in baseline characteristics were assessed with Chi² tests or Student's/Welch's T-tests when appropriate. The different echocardiogram parameters were assessed in the group as a whole and for men and women separately, these differences were assessed with Chi² tests. Adjusted odds ratio's were calculated using multiple logistic regression, with an abnormal echocardiogram (in which all abnormalities as described in Table 1 were taken together) as dependent variable. A possible relation

between an abnormal echocardiogram and systolic blood pressure (SBP) was adjusted for age, gender, education, current smoking, alcohol consumption, BMI, and diastolic blood pressure.

Results

Patient recruitment

From 5 different GP-practices, 913 eligible patients with hypertension were approached and 619 (68%) patients agreed to participate. Of these 619 participants, 2 were excluded because they were already being treated by a cardiologist, 5 were excluded because the echocardiogram was not of sufficient quality and 16 patients did not have an echocardiogram, 596 (65%) patients were included in the analysis.

Baseline characteristics

Table 2 shows the baseline characteristics, the mean age of the study patients was 70.4+/-6.5 years and the majority was female (56%,n=332). Men were more often higher educated and living together with a partner. Men were significantly more likely to have had a previous myocardial infarction, to consume more than 2 glasses alcohol a day on average, to have peripheral arterial disease, and to have higher diastolic blood pressure. Of the total sample, 67% had a SBP>140 mmHg (71% males, 64% females, p=.100), and 29% had a SBP>160 mm Hg (31% males, 27% females, p=.213) (figure 1). Mean SBP was 150+/-19.6 mmHg.

Figure 1. Systolic blood pressure categories in 596 elderly primary care patients with hypertension

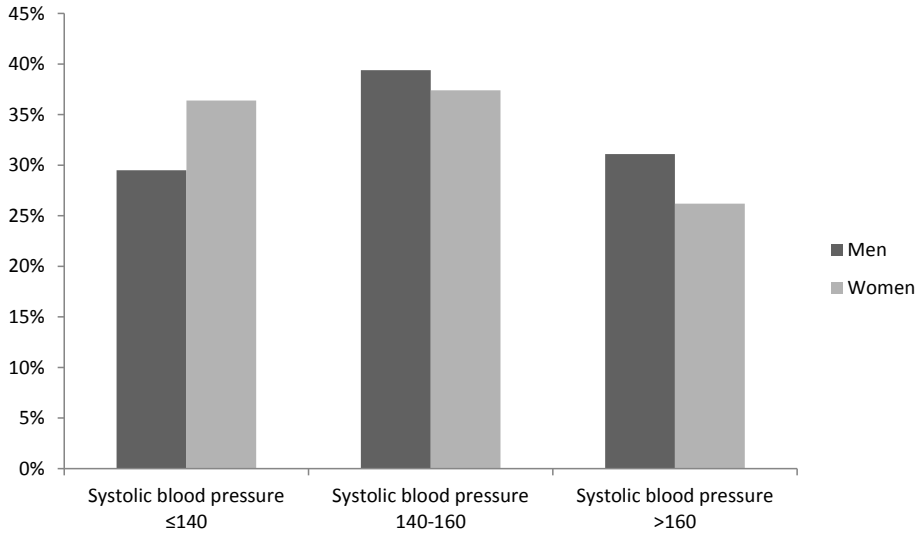

Table 2. Baseline characteristics of 596 elderly primary care hypertension patients

Characteristic	*Total, n=596*	*Male, n=264 (44%)*	*Female, n=332 (56%)*	*P-value*
Demographics				
Age, mean (SD)	69.9 (6.5)	69.3 (6.5)	70.4 (6.5)	.051
Low education	**77 (13%)**	**22 (8%)**	**55 (17%)**	**.003**
Having a partner	**447 (75%)**	**224 (85%)**	**223 (67%)**	**<.001**
Lifestyle				
Current smoker	77 (13%)	33 (13%)	44 (13%)	.785
Regular alcohol use (≥2 glasses per day)	**189 (32%)**	**120 (46%)**	**69 (21%)**	**<.001**
Clinical characteristics and risk factors				
Previous myocardial infarction	**28 (5%)**	**22 (8%)**	**6 (2%)**	**<.001**
Peripheral artery disease	**23 (4%)**	**15 (6%)**	**8 (2%)**	**.039**
TIA/Stroke	52 (9%)	27 (10%)	25 (8%)	.246
Diabetes type II	68 (11%)	35 (13%)	33 (10%)	.206
SBP (mmHg), mean (SD), n=591	150 (19.6)	151 (19.3)	148 (19.8)	.054
SBP>140 mmHg, n=591	397 (67%)	186 (71%)	211 (64%)	.100
SBP>160 mmHg, n=591	169 (29%)	82 (31%)	87 (27%)	.213
DBP (mmHg), mean (SD), n=591	**82.2 (10.5)**	**83.8 (10.1)**	**80.9 (10.7)**	**.001**
DBP>90 mmHg, n=591	**120 (20%)**	**65 (25%)**	**55 (17%)**	**.017**
Years since diagnosis of hypertension, mean (SD)	12.1 (10.8)	12.0 (10.5)	12.1 (11.0)	.613
BMI (kg/m2), mean (SD), n=592	28.0 (4.5)	27.8 (3.6)	28.2 (5.0)	.272

BMI, body mass index; TIA, transient ischemic attack

Abnormal echocardiogram

Table 1 shows the echocardiographic findings. In total, 181 (30%) of the patients had one or more cardiac abnormalities on the echocardiogram (32% males, 29% females, p=.493). A dilated left atrium, defined by a left atrium volume index of >29 ml/m², [13] was most prevalent (10%), this was more prevalent in females than in males (13% vs. 8%, p=.044). While a left atrium>29 ml/m² is described as abnormal, [13] a left atrium of ≥34 ml/m² can be an important independent predictor of death and heart failure. [14] Therefore we also report the prevalence of LAVI ≥34 ml/m², which was present in 37 patients (6%) (data not shown in table). A diminished LVEF (<55%) was observed in 9% of the patients, which was more prevalent in males than in females (11% vs. 6%, p=.029). LVH was observed in 6% of the patients, which was significantly more prevalent in males than in females (9% vs. 5%, p=.037). Diastolic dysfunction was observed in 6% of the patients. These 4 categories described above consisted of 22% of the total study population. Wall motion abnormalities were seen in 4% of the patients, with a significantly higher prevalence in males (9% vs. 1%, p<.001). When excluding patients with a previous MI, (n=28, n=22 males, n=6 females), 29% of the patients (n=164/568) had an abnormal echocardiogram, the prevalence of abnormal cardiac echo did not differ between men and women (p=.690, data not shown).

In table 3 the results of the multiple logistic regression analysis are shown with an abnormal echocardiogram as dependent variable and SBP as independent variable, after adjusting for age, gender, education, current smoking, alcohol consumption, BMI, and diastolic blood pressure. Higher age was significantly associated with abnormal echocardiogram (OR=1.07, 95% CI=1.03-1.10), as well as a SBP>160 mmHg (OR=1.57, 95% CI=1.03-2.38). When this analysis was repeated without patients with a history of MI, higher age and SBP>160 mmHg remained significantly and independently associated with an abnormal echocardiogram (higher age, OR=1.06, 95% CI=1.03-1.10; SBP>160 mmHg, OR=1.64, 95% CI=1.07-2.52).

Table 3. Multiple logistic regression, dependent variable: abnormal echocardiogram in 587 elderly primary care hypertension patients

Variable	*Odds ratio (95% CI)*	*P-value*
Female gender	.88 (.60-1.28)	.496
Age	**1.07 (1.03-1.10)**	**<.001**
Low education	.74 (.42-1.31)	.298
Current smoking	.58 (.31-1.06)	.077
Regular alcohol use (≥ 2 glasses per day)	.86 (.57-1.30)	.466
BMI	.99 (.94-1.03)	.528
DBP>90 mmHg	1.02 (.62-1.65)	.951
SBP>160 mmHg	**1.57 (1.03-2.38)**	**.034**

BMI, body mass index; DBP, diastolic blood pressure; SBP, systolic blood pressure.

Discussion

Principal findings

The results of this study show that 30% of the primary care hypertension patients in this study had an abnormal echocardiogram. A SBP >140 mmHg was observed in 67% of the patients, and 29% had a SBP >160 mmHg. A DBP >90 mmHg was observed in 20% of the patients. The most prevalent echocardiographic abnormalities were an enlarged left atrium, diminished LVEF, LVH, and diastolic dysfunction. Higher age and elevated SBP (>160 mmHg) were independently related to an abnormal echocardiogram. After excluding the patients with a history of myocardial infarction, the percentage of patients with an abnormal echocardiogram remained high (29%), and age and SBP remained significantly and independently related to an abnormal echocardiogram.

Comparison with previous reports

The prevalence of an enlarged left atrium is similar to findings of a previous study in patients without known cardiac disease who were referred for echocardiography.[16] In that study, an enlarged atrium (>29 ml/m^2) was also present in 10% of the patients. Although the study population was on average approximately 10 years younger, these patients were selected for echocardiography because of hypertension as well as palpitations, suspected valve disease, dyspnea, or chest discomfort.[16] It has previously been shown that an enlarged left atrium is a significant independent predictor of major adverse cardiac events.[17] Reduction of left atrial diameter resulting from antihypertensive treatment is associated with reduction in LVH and reduced incidence of atrial fibrillation and or mitral regurgitation.[18] A diminished LVEF in asymptomatic patients, which was found in 9% of the participants of the current study, is highly predictive for increased future cardiac morbidity and mortality.[19] In addition, LVH is an important predictor of cardiovascular events, and adequate antihypertensive treatment is associated with a decrease in left ventricular mass as well as reduced rates of cardiovascular death, myocardial infarction and stroke.[20] Diastolic dysfunction is also an independent predictor of cardiovascular events,[21] treatment with ACE inhibitors or ARBs is recommended.[22] Moreover, wall motion abnormalities in adults without clinically recognized cardiovascular disease are independently associated with future cardiovascular events.[23]

In general, no differences were found between males and females in the presence of an abnormal echocardiogram. However, when looking at the abnormalities in more detail, males and females differed in the prevalence of LAVI, LVH, and wall motion abnormalities. The difference in wall motion abnormalities can be explained by the significantly higher number of men with a history of a myocardial infarction, which is in agreement with previous studies.[23] Similar to our study, Katayama et al. showed a significantly higher LAVI

in women as compared to men in a sample of adults with normal ejection fraction.[24] In a review of echocardiographic studies on LVH in hypertensive patients, LVH was found in a high percentage of hypertensive patients (pooled range between 36%-41%), and no significant differences were found between men and women.[25] However, these patients were mostly selected and the prevalence varied widely, partly depending on the criteria used to diagnose LVH.[25] Comparable to several other studies,[6-8] blood pressure control in this study (SBP≤140 mmHg) was rather poor. The findings in the current study are comparable to a Finnish primary care study in which 35% of the hypertension patients had a SBP of ≤140 mmHg.[26] A Swiss primary care study showed that optimal blood pressure control was achieved in approximately 54%, which implies that higher numbers of optimal blood pressure control can be attainable.[27]

Strengths and limitations of the study

A major strength of this study was the focus on relatively healthy primary care patients, where preventive measures to reduce cardiac events are of importance. Furthermore, to our knowledge this study is the first to provide a clear overview of prevalence and associates of cardiac dysfunction on an echocardiogram in unselected elderly hypertension patients in primary care. Since hypertension is an important risk factor for cardiac disease, the results of screening on possibly modifiable cardiac abnormalities in a primary care population with hypertension with an echocardiogram are very relevant for cardiovascular risk management and prevention. The course of the abnormalities may be favorably altered with adequate treatment, resulting in prevention of heart failure and other cardiac disease.[5,28] In addition, echocardiography is easily accessible, cheap, and an acceptable and simple method for screening patients in general.[2,4]

Some limitations of the study should be mentioned. First, the results may not be generalized to other settings than primary care. However, most of the hypertension patients are preferentially seen in primary care, the results of this study are relevant for a large group of hypertension patients. Since the Framingham study showed that 90% of people aged 55 years without elevated blood pressure will eventually develop hypertension,[1] hypertension patients represent a large group. Second, we used a simplified protocol to define cardiac abnormalities on the echocardiogram. Since the echocardiograms were all performed in the local general practices, a simpler screening echocardiogram was suitable. In case of need for further detailed assessment of cardiac dysfunction, patients were referred to a cardiologist in a hospital. Third, this is a cross-sectional study, which limits the possibility to report the impact of the cardiac abnormalities found in this screening on future cardiovascular events. However, other prospective studies already have indicated the association of the specific abnormal echocardiograms also found in the current study and the development of future

cardiovascular events such as atrial fibrillation and cardiovascular death.[18-21,23,29] Although the echocardiogram is cheap, and easy to perform at the GP office, the cross-sectional design does not allow for an adequate cost-effectiveness analysis. However, given the fact that most of the abnormal echocardiograms could be accompanied by a simple medication change advice to the GP (higher dose or change to other regimens were given in 48% of the patients with an abnormal echocardiogram, 15% of the total study population) which has been shown to improve future cardiovascular health, the findings in the current cross-sectional study seem promising with regard to cost-effectiveness.

Clinical implications

In the current study, most of the adapted World Health Organization criteria of screening of Wilson and Jungner are met.[30] Hypertension is a highly prevalent condition, the screening instrument is cheap and non-invasive, user friendly offered at the primary care office. Moreover, interventions are available (change of medication regimens) which have repeatedly been shown in prospective follow-up studies to markedly improve cardiovascular outcomes.[18,20,22] An abnormal echocardiogram is a major risk factor to develop heart failure with poor prognostic outcome.[17,19-21] Up to 2/3 of the primary care hypertension patients do not meet optimal blood pressure cut-offs suggesting that there is still a way to go in primary care cardiovascular risk management, especially because high SBP was independently related to an abnormal echocardiogram.

Conclusions

This study detected an unexpectedly high prevalence of abnormal echocardiograms in unselected elderly primary care hypertension patients. Previous research has shown that these cardiac abnormalities are associated with poor cardiac outcomes, and adequate treatment can improve prognosis. Screening of all elderly hypertension patients by means of an echocardiogram should be considered.

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Chapter 4

Symptoms Associated with an Abnormal Echocardiogram in Elderly Primary Care Hypertension Patients

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Abstract

Background: The prevalence and diagnostic value of heart failure symptoms in elderly primary care patients with hypertension is unknown.

Aim: To assess the prevalence, sensitivity, specificity, positive, and negative predictive value of symptoms in association with an abnormal echocardiogram.

Design and setting: Cross-sectional screening study in five general practices in the South-East of The Netherlands.

Method: Between June 2010 and January 2013, 591 primary care hypertension patients aged between 60 and 85 years were included, without known heart failure and not treated by a cardiologist. All patients underwent an echocardiogram and a structured interview including assessment of heart failure symptoms; shortness of breath, fatigue, oedema, cold extremities, and restless sleep.

Results and conclusion: Restless sleep was reported by 25%, cold extremities by 23%, fatigue by 19%, shortness of breath by 17%, and oedema by 13%. Oedema was the only symptom significantly associated with an abnormal echocardiogram (positive predictive value was 45%, sensitivity 20%, and specificity 90%, OR 2.12; 95% CI=1.23-3.64), apart from higher age (OR 1.06; 95% CI=1.03-1.09), previous myocardial infarction (OR 3.00; 95% CI=1.28-7.03), and a systolic blood pressure of >160 mmHg (OR 1.62; 95% CI=1.08-2.41). Screening with echocardiography might be considered in patients with oedema.

Introduction

Hypertension is highly prevalent, with the Framingham study showing a lifetime risk for developing hypertension of 90% in people with a normal blood pressure at age 55.[1] A high blood pressure can result in coronary artery disease and changes in ventricular function and structure,[2] and is a major risk factor for incident heart failure,[3] with a five-year survival rate of 35% according to previous research.[4] Early diagnosis and treatment of heart failure are crucial for reducing heart failure related morbidity and mortality.[5-7] General practitioners (GPs) are most frequently involved in the diagnosis of heart failure.[8] More severe hypertension in primary care patients is associated with a higher risk of cardiovascular events,[9] and lowering blood pressure can reduce risk of major cardiovascular events.[10] However, in less than 50% of patients above the age of 65 hypertension is properly managed.[11-13] Therefore, elderly hypertension patients, especially those with less than optimal blood pressure, are at high risk for heart failure.

Several important patient-reported symptoms of heart failure are oedema, dyspnea, and fatigue.[14-16] Because most patients with possible heart failure will present themselves first in primary care,[16] it is important for a GP or practice nurse (PN) to identify symptoms predictive of this condition. However, most studies on symptoms used for assessment of heart failure have focused on hospital populations[8] and/or on patients who presented themselves with dyspnea,[17,18] or had suspected heart failure.[19] Furthermore, the majority of studies evaluated symptoms only in association with left ventricular systolic dysfunction and did not take other relevant abnormalities such as diastolic function into account.[5,8] Left ventricular hypertrophy (LVH), an enlarged left atrium, valvular heart disease, and wall motion abnormalities can also be major causes of heart failure and are related to coronary artery disease.[20-22]

Echocardiography is seen as the gold standard for the diagnosis or confirmation of cardiac dysfunction associated with heart failure[5] and can be used to detect cardiac abnormalities.[2] Although the diagnostic value of symptoms and signs of heart failure has been topic of debate[17], attention to symptoms can still be of relevance in patients at risk for heart failure.[5]

Until now it is unclear in elderly primary care hypertension patients which heart failure symptoms may be associated with an abnormal echocardiogram. The objectives of the current study were to examine (1) the prevalence of symptoms which are in general related to cardiac dysfunction reflected by an abnormal echocardiogram, (2) the sensitivity, specificity, positive, and negative predictive value of symptoms of an abnormal echocardiogram, and (3) the relation between the symptoms and an abnormal echocardiogram, after adjustment for several confounders.

Methods

Study design and patient population

Between June 2010 and January 2013, primary care patients aged between 60-85 years, with an International Classification of Primary Care for hypertension (K86 or K87) as captured from their medical record, were recruited from five general practices affiliated with the primary care organization PoZoB (a primary care organisation of approximately 200 GPs, located in the South of The Netherlands) for this cross-sectional study. Exclusion criteria were: previous diagnosis of heart failure, current treatment by a cardiologist, history of severe psychiatric illness other than mood/anxiety disorders and/or cognitive impairments (e.g. dementia), terminal cancer, and insufficient knowledge of the Dutch language. This study was approved by the medical ethics committee of the Elisabeth Hospital in Tilburg, The Netherlands.

Study procedure and data collection

Eligible patients received written information about the study by mail and were asked to sign an informed consent form. In case of informed consent patients were contacted, and an appointment for an interview at their local GP office was scheduled. This interview consisted of a structured interview of one hour by a trained nurse. At the end of the intake, an appointment for the echocardiogram was scheduled which also took place at the local GP office.

Measurements

Demographic and clinical variables

Information on demographic and clinical variables was obtained from purpose-designed questions in the interview and included gender, age, marital status, and educational level. Furthermore, blood pressure was measured twice and the average blood pressure was used to dichotomize systolic blood pressure (>160 mmHg was cut-off). Height and weight were measured in order to calculate the body mass index (BMI). Information on clinical variables retrieved from the patients' medical records included myocardial infarction (MI) and peripheral arterial disease.

Assessment of symptoms

Information on heart failure symptoms was obtained during the interview. Structured and standardized questions were used to assess heart failure symptoms. Symptoms were dichotomized (yes/no) and defined as; shortness of breath during moderate exertion (e.g. walking), regularly occurring fatigue, oedema of the legs, ankles and/or feet, having cold extremities, and restless sleep, during the past 4 weeks.

Assessment of the echocardiogram

The echocardiogram was performed and evaluated by an experienced echocardiographist of the local primary care laboratory located in Eindhoven, The Netherlands. All the echocardiograms were reviewed by a cardiologist specialized in echocardiography, who indicated if the echocardiogram was abnormal according to a protocol suitable for primary care, based on current guidelines.[23,24] The definition of an abnormal echocardiogram is shown in Table 1.

Table 1. Prevalence of abnormal echocardiogram parameters in 591 elderly primary care hypertension patients

	Total (n=591)
Abnormalities on the echocardiogram	
LAVI > 29 ml/m²	60 (10%)
LVEF <55%	51 (9%)
Valvular abnormalities	48 (8%)
LVH septal and posterior wall thickness of ≥ 13 mm (moderate or severe)	36 (6%)
Diastolic dysfunction (E/A ratio of <1 and DTs of >200ms, and presence of LVH in case of grade I diastolic dysfunction)	35 (6%)
Wall motion abnormalities (hypokinesia, akinesia and dyskinesia)	26 (4%)
RVH; subcostal wall thickness of ≥6mm (mild, moderate or severe)	15 (3%)
Total ≥1 abnormality	*175 (30%)*

LAVI, left atrial volume index; LVEF, left ventricular ejection fraction; LVH, left ventricular hypertrophy; RVH, right ventricular hypertrophy; DT, deceleration time

Statistical analyses

Statistical analyses were performed using the IBM Statistical Package for the Social Sciences version 18.0. Differences in baseline characteristics were compared between normal and abnormal echocardiogram and assessed with Chi-square tests or Student's/Welch's T-tests when appropriate. For each symptom and clinical variable, the sensitivity, specificity, positive predictive value, and negative predictive value with 95% confidence intervals were calculated.

Adjusted odds ratio's were calculated using multiple logistic regression, with an abnormal echocardiogram (taking all cardiac abnormalities together) as dependent variable. A possible relation between symptoms and an abnormal echocardiogram were adjusted for age, gender, education, having a partner, previous MI, peripheral arterial disease, and elevated systolic blood pressure of >160 mmHg.

Results

Patient recruitment

From 6 different GP-practices, 913 eligible patients with hypertension were approached and 619 (68%) patients agreed to participate. Of these participants, 2 were excluded post-hoc because they met the exclusion criterion of being treated by a cardiologist, 5 were excluded post-hoc because the echocardiogram was not of sufficient quality and 16 patients did not have an echocardiogram. Patients with congenital disease and/or hypertrophic cardiomyopathy were excluded from analyses (n=5), leaving a total of 591 (65%) patients for analysis.

Baseline characteristics

Table 2 shows the baseline characteristics. The mean age of the study patients was 70+/-6.5 years and 44% was male (n=262). Patients with an abnormal echocardiogram were significantly older, did less often have a partner, were more likely to have had a previous MI, and had a higher systolic blood pressure as compared to the patients with a normal echocardiogram. Abnormalities on the echocardiogram were present in 30% of the study sample (Table 1).

Heart failure symptoms and abnormal echocardiogram

Restless sleep was the most prevalent symptom (25%, n=149). The most sensitive was shortness of breath with a sensitivity of 32%. The most specific symptom was oedema of the ankles, feet, or legs, with a high specificity of 90%. Oedema did also have the highest positive predictive value (45%) and negative predictive value (73%) for an abnormal echocardiogram (Table 3).

In adjusted analysis (Table 4), oedema was significantly and independently related to an abnormal echocardiogram adjusted for age, sex, having a partner, the co-existence of type 2 diabetes or peripheral arterial disease, systolic blood pressure >160 mmHg. The other symptoms were not significantly associated with an abnormal echocardiogram in adjusted analysis.

Table 2. Baseline characteristics of 591 elderly primary care hypertension patients

Characteristic	*Total, N=591*	*Normal echocardiogram, N=416*	*Abnormal echocardiogram, N=175*	*P-value*
Demographics				
Male	262 (44%)	180 (43%)	82 (47%)	.423
Age, mean (SD)	**69.9 (6.5)**	**69.1 (6.1)**	**72.0 (7.0)**	**<.001**
Low education	76 (13%)	55 (13%)	21 (12%)	.686
Having a partner	**443 (75%)**	**324 (78%)**	**119 (68%)**	**.011**
Lifestyle				
Current smoker	77 (13%)	61 (15%)	16 (9%)	.069
Regular alcohol use (≥ 2 glasses per day)	188 (32%)	133 (32%)	55 (31%)	.897
Clinical characteristics and risk factors				
Previous myocardial infarction	**27 (5%)**	**11 (3%)**	**16 (9%)**	**.001**
Peripheral artery disease	23 (4%)	12 (3%)	11 (6%)	.051
TIA/Stroke	52 (9%)	33 (8%)	19 (11%)	.252
Diabetes type 2	67 (11%)	45 (11%)	22 (13%)	.539
Mean systolic blood pressure (mmHg), mean (SD) (N=587)	**150 (19.6)**	**147 (18.0)**	**155 (22.2)**	**<.001**
Systolic blood pressure >160 mmHg (N=587)	**168 (29%)**	**104 (25%)**	**64 (37%)**	**.005**
Mean diastolic blood pressure (mmHg), mean (SD) (N=587)	82.2 (10.5)	82.0 (10.3)	82.8 (10.9)	.351
Diastolic blood pressure >90 mmHg (N=587)	120 (20%)	83 (20%)	37 (21%)	.784
BMI (kg/m2), mean (SD)	28.0 (4.5)	28.1 (4.6)	27.7 (4.1)	.356

TIA, transient ischemic attack; BMI, body mass index

Table 3. Sensitivity, specificity, positive predictive value, negative predictive value of symptoms associated with an abnormal echocardiogram (N=175/591, 30%)

	N (%)	*Sensitivity*	*95% CI*	*Specificity*	*95% CI*	*PPV*	*95% CI*	*NPV*	*95% CI*
Shortness of breath	102 (17%)	32.3%	14.3%-20.6%	71.0%	66.6%-74.9%	29.6%	26.0%-33.5%	70.4%	66.5%-74.0%
Fatigue	110 (19%)	20.6%	15.0%-27.5%	82.2%	78.1%-85.7%	32.7%	24.3%-42.4%	71.1%	66.8%-75.1%
Oedema of ankles, feet, legs	78 (13%)	20.0%	14.5%-26.9%	89.7%	86.2%-92.3%	44.9%	33.7%-56.5%	72.7%	68.6%-76.4%
Cold extremities	137 (23%)	28.0%	21.6%-35.4%	78.8%	74.5%-82.6%	35.7%	27.9%-44.4%	72.2%	67.8%-76.3%
Restless sleep	149 (25%)	22.9%	17.0%-29.9%	73.8%	69.2%-77.9%	26.8%	20.0%-34.8%	69.5%	64.9%-73.7%

NPV, negative predictive value; PPV, positive predictive value

Table 4. Correlates of abnormal echocardiogram in elderly primary care hypertension patients (adjusted analysis; N=587)

Unadjusted analysis	***Odds ratio (95% CI)***	***P-value***
Demographics		
Female gender	.87 (.61-1.23)	.423
Age	**1.07 (1.04-1.10)**	**<.001**
Having a partner	**.60 (.41-.89)**	**.012**
Clinical history		
Previous myocardial infarction	**3.71 (1.68-8.16)**	**.001**
Peripheral arterial disease	2.26 (.98-5.22)	.057
Systolic blood pressure >160 mmHg	**1.70 (1.16-2.49)**	**.006**
Symptoms		
Shortness of breath	1.17 (.74-1.85)	.505
Fatigue	1.20 (.77-1.87)	.428
Oedema of lower extremities	**2.17 (1.33-3.53)**	**.002**
Cold extremities	1.45 (.97-2.17)	.073
Restless sleep	.84 (.55-1.26)	.393
Adjusted analysis	***Odds ratio (95% CI)***	***P-value***
Demographics		
Female gender	.83 (.56-1.25)	.378
Age	**1.06 (1.03-1.09)**	**<.001**
Having a partner	.71 (.46-1.11)	.135
Clinical history		
Previous myocardial infarction	**3.00(1.28-7.03)**	**.011**
Peripheral arterial disease	1.44 (.70-4.37)	.230
Systolic blood pressure >160 mmHg	**1.62 (1.08-2.41)**	**.019**
Symptoms		
Shortness of breath	.90 (.53-1.53)	.702
Fatigue	.92 (.54-1.56)	.763
Oedema of lower extremities	**2.12 (1.23-3.64)**	**.007**
Cold extremities	1.30 (.84-2.01)	.240
Restless sleep	.95 (.61-1.50)	.836

Discussion

The current study shows that regular restless sleep was reported by 25%, having cold extremities by 23%, fatigue by 19%, shortness of breath by 17%, and oedema of legs, ankles and/or feet by 13%. An abnormal echocardiogram was present in 30%. Oedema is an important symptom of cardiac dysfunction as reflected by an abnormal echocardiogram; the positive predictive value of oedema was 45%, the sensitivity 20%, and specificity 90%. In adjusted analysis, oedema was the only symptom that was significantly associated with abnormal echocardiogram apart from higher age, previous MI, and a systolic blood pressure of >160 mmHg. The symptoms shortness of breath, fatigue, having cold extremities, and having restless sleep were of limited value in predicting an abnormal echocardiogram.

Strengths and limitations

This study is among the first to evaluate the value of heart failure symptoms in the diagnosis of cardiac dysfunction in unselected elderly primary care hypertension patients. Since hypertension is one of the most important risk factors for incident heart failure[3] and elderly hypertension patients represent a large proportion of patients in whom cardiovascular risk management is crucial, the results of this study are very relevant. Furthermore, by using echocardiography, we studied the association between symptoms and cardiac abnormalities associated with heart failure including left ventricular dysfunction, diastolic dysfunction, LVH, and valvular dysfunction, while a majority of research evaluated the association of symptoms and left ventricular systolic dysfunction only, not taking into account other cardiac dysfunctions predictive of heart failure.[8]

Some methodological issues need consideration. First, the cross-sectional design of the study does not allow for evaluation of the course of symptoms in relation to cardiac dysfunction. Second, the study population was primarily Caucasian (99%) limiting generalizability to other populations with more ethnic diversity. Another limitation is that we do not have detailed demographic information of the non-responders. However, the response rate in the current study was almost 70%. Moreover, the current design was not used to assess prevalence figures but rather to evaluate whether signs and symptoms could be associated with echocardiogram outcome.

Comparison with existing literature

Previous research showed that the most common symptoms associated with heart failure are oedema, dyspnea, and fatigue.[14,15] However, most previous studies looking at the value of symptoms in the diagnosis of heart failure used selected samples of patients who were referred because of symptoms, mostly including patients who already reported dyspnea.[25] For example, patients in the study of Davie et al. were referred for diagnosis of heart failure and the large majority was referred because of symptoms (dyspnea), and the symptom oedema had no predictive value and low sensitivity and specificity.[19] In another primary care study in patients with suspected heart failure based on a questionnaire and a physical examination, similar findings were reported; oedema had limited value in the diagnosis of heart failure, and as in the current study no other symptoms were associated with heart failure diagnosis.[17] However, the latter study excluded patients who visited for a specialized consultation including hypertension consults, which limits the possibility to generalize the results to hypertension patients. Furthermore, other studies assessing the diagnostic accuracy of dyspnea found heterogeneous results, and conclude that symptoms and signs are of limited use for ruling out heart failure primarily because of a low sensitivity.[25] Especially in early stages of heart failure, milder symptoms do occur which are generally

insensitive in the diagnosis of heart failure.[6] Nevertheless, a diagnostic tool for heart failure in primary care was developed, based on a systematic review. According to this research, patients who present themselves with symptoms of heart failure (e.g. breathlessness) are most at risk when there is a history of MI, basal crepitations present, and the patient is male with ankle oedema. The inclusion of oedema in this tool is more in line with our findings, however, this tool was developed for populations of patients with already suspected heart failure with presentation of symptoms,[26] and therefore this tool is most likely not suitable for unselected elderly primary care hypertension patients.

Although breathlessness is the most commonly reported symptom in established heart failure in primary care,[16] our findings showed that oedema, and not shortness of breath, was significantly and independently associated with cardiac dysfunction as reflected by an abnormal echocardiogram, together with previous MI, higher age, and elevated systolic blood pressure. However, oedema had a low sensitivity making it less useful for ruling out cardiac dysfunction in elderly hypertension patients. The low sensitivity of all symptoms in our study can possibly be explained by the mild severity of cardiac dysfunction, with the majority of patients not reporting any symptoms.

Implications

In the majority of cases the GP is involved in the initial diagnosis of heart failure.[16] Therefore, attention to cardiac dysfunction predictive of chronic heart failure is important, especially in primary care populations at increased risk. The echocardiogram is the most useful test in the assessment of chamber volumes, systolic, and diastolic function,[6] and it is recommended by recent guidelines as a useful tool to evaluate LVH and left ventricular dysfunction.[2] The results of our study show that oedema of the lower limbs is significantly associated with cardiac dysfunction on an echocardiogram in elderly hypertension patients, it has modest positive predictive value, but adequate specificity. Although the value of symptoms is limited in the diagnosis of heart failure,[17] oedema of the lower limbs could be of diagnostic value. The presence of oedema in elderly hypertension patients could alert the GP to initiate further assessment of cardiac function by means of echocardiography. To conclude, it would be recommended for GPs to check for oedema and consider an echocardiogram for further diagnosis of cardiac dysfunction, especially in elderly hypertension patients with a poorly controlled systolic blood pressure and/or a previous MI.

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Chapter 5

Prevalence of Psychological Distress in Elderly Hypertension Patients in Primary Care

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Abstract

Background: Recent guidelines on cardiovascular disease prevention advocate the importance of psychological distress, as they contribute to the risk of developing cardiovascular disease. However, most previous research on psychological distress and cardiovascular factors has focused on selected populations with cardiovascular disease.

Aim: The primary aim was to determine the prevalence of depression, anxiety, and Type D personality in elderly primary care patients with hypertension. The secondary aim was to examine the relation between elevated systolic blood pressure and depression, anxiety, and Type D personality.

Design and Setting: A cross sectional study in primary care practices located in the South of the Netherlands.

Method: Primary care hypertension patients (n=605), between 60-85 years (45% men, mean age=70±6.6), were recruited for this study. All patients underwent a structured interview including validated self-report questionnaires to assess depression (PHQ-9), anxiety (GAD-7), and Type D personality (DS14) as well as blood pressure assessment.

Results and Conclusion: Depression was prevalent in 5%, anxiety in 5%, and Type D personality in 8%. None of the distress measures were associated with elevated systolic blood pressure of >160 mmHg (all p-values >0.05). This study showed no relation between psychological distress and elevated systolic blood pressure in elderly primary care patients with hypertension.

Introduction

Hypertension is an important risk factor for cardiovascular disease, such as coronary artery disease (CAD), heart failure and stroke[1] with the mean prevalence of hypertension in six European countries being 44% (50% in men, 39% in women).[2] Systolic blood pressure increases with age, with the mean systolic blood pressure (SBP) of European citizens aged 60-64 years exceeding 140 mmHg, which increases to a mean SBP of 150 mmHg for those aged 70-74 years.[2]

One of the key messages in the 2012 European guidelines on cardiovascular disease prevention in clinical practice is that assessment of psychosocial factors such as depression, anxiety, and Type D personality (the tendency to experience negative emotions combined with the tendency to inhibit expression of emotions[3]) in patients with cardiovascular disease (CVD) risk factors is crucial, as they contribute to the risk of developing CVD.[4] However, more recent and larger studies have reported smaller or no effects of Type D personality on cardiovascular outcomes or mortality as compared to earlier studies.[5] A recent systematic review showed an increased incidence of hypertension in individuals with elevated symptoms of depression.[6] In contrast with the European guidelines[4] and cardiac rehabilitation where screening for anxiety and/or depression is recommended,[7] psychological factors are not included in the multifactorial[8] Dutch primary care guidelines on Cardiovascular Risk Management.[9]

In patients with hypertension, psychological distress may serve as a barrier against adequate medication adherence.[10] Prior findings have shown an independent association between poor medication adherence in elderly patients with hypertension and depression and anxiety.[10,11] In general, adherence is considered paramount for the successful treatment of hypertension, with non-adherence as one of the possible causes of resistant hypertension.[12]

The objectives of the current study were to examine (1) the prevalence of symptoms of depression, anxiety and Type D personality in elderly primary care patients with hypertension, and (2) the relation between elevated symptoms of depression, anxiety, Type D personality, and systolic blood pressure.

Methods

Participants and design

Between June 2010 and January 2012, primary care patients aged between 60-85 years with diagnosed hypertension according to their medical records were recruited for this cross-

sectional study from five general practices affiliated with the primary care organization PoZoB. Exclusion criteria were: Previous diagnosis of heart failure, current treatment by a cardiologist, history of severe psychiatric illness other than mood or anxiety disorders, cognitive impairments, terminal cancer, insufficient knowledge of the Dutch language, illiteracy, or inability to read due to visual impairments. The study protocol was approved by the medical ethics committee of the Elisabeth Hospital, Tilburg, The Netherlands. All participants provided informed consent.

Measures

Demographic and clinical variables

Demographic variables assessed during a structured interview at the local general practitioner (GP) office included age, gender, education level, and marital status. Clinical variables assessed during the structured interview included height, weight, blood pressure (after 20 and 40 minutes of resting), current smoking, alcohol consumption, current or past depression, and current or past anxiety. Information on clinical variables obtained via chart extraction and using International Classification of Primary Care codes were previous myocardial infarction, peripheral arterial disease, cerebrovascular accident or transient ischemic attack (CVA/TIA), chronic obstructive pulmonary disease (COPD), type 2 diabetes, and years since diagnosis of hypertension.

Psychological measures

Psychological distress was assessed with patient-report questionnaires which were filled out during the structured interview. The 14-item Type D Scale (DS14) was used to assess Type D personality with 7 items tapping into negative affectivity (NA) and 7 items into social inhibition (SI). Items are rated on a 5-point Likert scale. The SI and NA scales can be used as continuous scales (range 0-28), and also to classify patients as “Type D” versus “non-Type D”, using a cut-off of 10 on both NA and SI that was found to be optimal according to item response theory.[13] The DS14 is a valid and reliable instrument to assess Type D personality.[14] Symptoms of depression were measured with the Patient Health Questionnaire-9 (PHQ-9). The nine items are rated on a 4-point Likert scale (range 0-27). For this study a cut off of ≥9 was used, since it is considered suitable for elderly individuals in primary care, with a sensitivity of .88 and specificity of .80, and an area under the curve for the detection of a major depressive disorder of .87.[15] Symptoms of anxiety were measured with the Generalized Anxiety Disorder-7 (GAD-7) scale. The seven items are rated on a 4-point Likert scale (range 0-21). A cut-off of ≥8 has a high sensitivity and specificity for the detection of generalized anxiety disorder (sensitivity=.92 and specificity=.76) as well as for the detection of any anxiety disorder (sensitivity=.77 and specificity=.82), the area under the curve for detecting generalized anxiety disorder is .91.[16]

Both the PHQ-9 and the GAD-7 are derived from the Primary Care Evaluation of Mental Disorders (PRIME-MD), which was originally designed for the diagnosis of five mental disorders (depression, anxiety, alcohol abuse, somatoform disorder, and eating disorder) in the primary care setting by using DSM IV criteria.[17]

Statistical analyses

Statistical analyses were performed using IBM Statistical Package for the Social Sciences version 18.0. Because previous research has shown differences in prevalence of depression and anxiety between men and women, the different psychological indices are reported for the total group and for men and women separately.[18] Student's t-tests or Welch's t-tests (two-tailed) were used to assess differences in mean scores between groups when appropriate. Unadjusted odds ratio's were calculated using univariable logistic regression analysis, with an elevated systolic blood pressure >160 mmHg as dependent variable which was calculated using the mean of the two blood pressure assessments. Adjusted odds ratio's were calculated using multiple logistic regression, also with an elevated systolic blood pressure >160 mmHg as dependent variable and elevated symptoms of depression, anxiety, and Type D personality, as independent variables, adjusting for age, gender, having a partner, education, current smoking, alcohol consumption, and BMI.

Results

Of 913 patients with hypertension approached, 619 (68%) agreed to participate. Fourteen patients were excluded post-hoc as they met the exclusion criterion of being treated by a cardiologist (n=2), missing all PHQ-9, GAD-7, and DS14 scores (n=1), and insufficient knowledge of the Dutch language (n=11). This resulted in 605 patients (66%) that could be included in the analyses. The baseline characteristics for the total sample and stratified by systolic blood pressure ≤160 mmHg and >160 mmHg, are shown in Table 1. The mean age was 70 years (±6.6) and 45% of the study population was male.

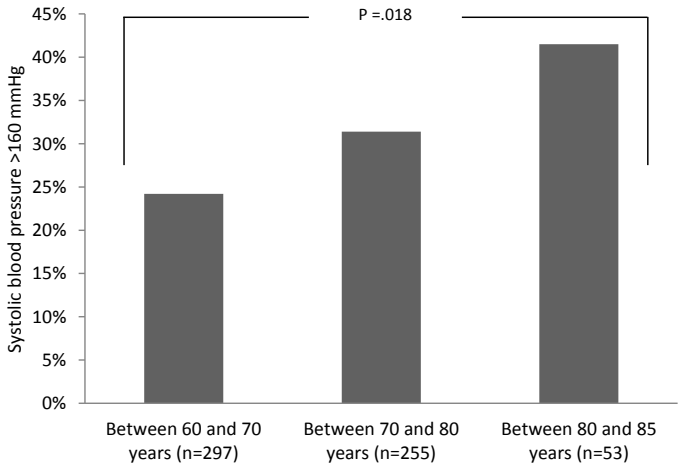
An elevated systolic blood pressure of >160 mmHg was found in 29% of the patients (n=174). A systolic blood pressure of >160 mmHg was associated with higher age (p=.006), regular alcohol consumption (p=.006), and an elevated diastolic blood pressure of >90 mmHg (p<.001). Using the age categories 60-70 years, 70-80 years, and 80-85 years, prevalence of elevated systolic blood pressure increased significantly with age (p=.018, Figure 1). The proportion of males and females was similar in both participants and non-participants. Women who refused participation were significantly older (p < .001).

Table 1. Baseline characteristics for the total sample and stratified by systolic blood pressure

Characteristic	*Total sample (n=605)*	*SBP≤160 (n=431)*	*SBP>160 (n=174)*	*P-value*
Demographics				
Male	270 (45%)	186 (43%)	84 (48%)	.251
Age (mean ± SD)	**70.0 (6.6)**	**69.5 (6.5)**	**71.1 (6.5)**	**.006**
Having a partner	455 (75%)	323 (75%)	132 (76%)	.812
Low educational level	78 (13%)	50 (12%)	28 (16%)	.136
Risk factors				
Smoking	81 (13%)	55 (13%)	26 (15%)	.476
Alcohol consumption ≥ 2 glasses a day (on average)	**194 (32%)**	**124 (29%)**	**70 (40%)**	**.006**
BMI kg/m² (mean ± SD, n=600)	28.0 (4.4)	28.1 (4.5)	27.9 (4.2)	.628
Medical history				
Years since diagnosis (mean ± SD)	12.3 (11.2)	11.8 (10.2)	13.6 (13.1)	.105
Diastolic blood pressure >90 mm/Hg	**126 (21%)**	**52 (12%)**	**74 (43%)**	**<.001**
Previous myocardial infarction	27 (5%)	20 (5%)	7 (4%)	.739
Peripheral arterial disease	23 (4%)	15 (4%)	8 (5%)	.515
TIA/stroke	55 (9%)	38 (9%)	17 (10%)	.712
Diabetes type II	68 (11%)	52 (12%)	16 (9%)	.312

SBP, systolic blood pressure; BMI, body mass index; TIA, transient ischemic attack

Figure 1. Elevated systolic blood pressure in three age categories



As shown in Table 2, the prevalence of depression using a cut-off score of (≥9) on the PHQ-9 was 5%, of anxiety using a cut-off of ≥8 on the GAD-7 5%, and of Type D personality 8% when using a cut-off of ≥10 on both the negative affectivity and social inhibition subscales of the DS14. Women had significantly higher mean depression, anxiety, and negative affect scores than men.

Table 2. Prevalence and mean scores of depression, anxiety, and Type D in 605 elderly primary care hypertension patients stratified by gender

	Total sample	*Men*	*Women*	*P-value*
Prevalence				
Depression (PHQ-9 ≥9)	**30 (5%)**	**6 (2%)**	**24 (7%)**	**.006**
Anxiety (GAD-7 ≥8)	31 (5%)	11 (4%)	20 (6%)	.293
Type D personality*	**49 (8%)**	**15 (6%)**	**34 (10%)**	**.041**
Mean scores				
Depression symptoms (PHQ-9 total score)	**2.2 (3.0)**	**1.5 (2.4)**	**2.7 (3.4)**	**<.001**
Anxiety symptoms (GAD-7 total score)	**1.9 (2.9)**	**1.4 (2.6)**	**2.2 (3.1)**	**.001**
DS14 negative affect	**4.3 (4.8)**	**3.2 (4.3)**	**5.1 (5.1)**	**<.001**
DS14 social inhibition	6.0 (5.7)	5.7 (5.3)	6.3 (5.9)	.207

*a score of ≥10 on both the negative affect and social inhibition subscales

In the unadjusted analysis (Table 3), age (OR=1.038, 95% CI=1.010-1.066) and regular alcohol consumption (OR=1.666, 95% CI=1.154-2.407) were significantly associated with a systolic blood pressure of >160 mmHg. Depression, anxiety and Type D personality were not related to high systolic blood pressure. Adjusted logistic regression showed that age (OR=1.042, 95% CI=1.011-1.073) and regular alcohol consumption (OR=1.661, 1.121-2.426) were significantly related to a systolic blood pressure of >160 mmHg (Table 3). Again there was no association with depression, anxiety, and Type D personality, adjusting for age, gender, marital status, low education, current smoking, regular alcohol consumption, and BMI.

Table 3. Associates of systolic blood pressure of >160 mmHg in elderly primary care hypertension patients

Unadjusted analysis	***OR***	***95% CI***
Female gender	.813	.571-1.158
Age	**1.038**	**1.010-1.066**
Having a partner	1.051	.697-1.583
Low education	1.461	.886-2.410
Current smoking	1.201	.726-1.988
Alcohol consumption ≥ 2 glasses a day (on average)	**1.666**	**1.154-2.407**
BMI	.990	.951-1.031
Type D personality*	1.347	.727-2.495
Depression (PHQ-9 ≥9)	.907	.396-2.078
Anxiety (GAD-7 ≥8)	.855	.375-1.950
Adjusted analysis		
Female gender	.879	.598-1.293
Age	**1.042**	**1.011-1.073**
Having a partner	1.300	.821-2.059
Low education	1.425	.837-2.428
Current smoking	1.416	.826-2.428
Alcohol consumption ≥ 2 glasses a day (on average)	**1.661**	**1.121-2.462**
BMI	.999	.958-1.041
Type D personality*	1.563	.805-3.038
Depression (PHQ-9 ≥9)	.950	.370-2.437
Anxiety (GAD-7 ≥8)	.863	.339-2.196

*a score of ≥10 on both the negative affect and social inhibition subscales

Discussion

The results of this study indicate a low prevalence of psychological distress in an unselected sample of elderly primary care hypertension patients. Elevated symptoms of depression were found in 5%, elevated symptoms of anxiety in 5%, and Type D personality was prevalent in 8% of the study population. We found no association between elevated symptoms of depression, anxiety, Type D personality and an elevated systolic blood pressure.

The prevalence of depression in the current study is in line with a large study on depression in later life in which the prevalence of depression in adults aged between 55 and 85 years was 2% for major depressive disorder and 13% for minor depression.[19] In general up to 50% of patients with moderate to high scores on the PHQ-9 do have a major depression,[20] which would imply that 2.5% of the patients in the current study could have a major depression. A review on generalized anxiety disorder in primary care has indicated a prevalence between 3% and 9%, which is similar to our findings.[21] Results of a population based study showed a decline in the prevalence of depression, anxiety, and Type D personality with higher age. This is in line with our results on the prevalence of depression and anxiety, however, Type D personality was prevalent in 17% of their study population of elderly individuals which is more than twice as much as compared to our study.[22] Another previous study on Type D personality, also in primary care hypertension patients with a mean age of 60, found a very high prevalence of Type D personality (53%).[14] This is in contrast to our findings of a Type D prevalence rate of only 8%. Another Dutch population based study showed a prevalence of Type D personality of 13%,[23] which is more in line with the results of our study, indicating that prevalence rates of Type D personality may vary markedly amongst different studies and populations.

The 2012 European guidelines on cardiovascular disease prevention underline the importance of psychological factors in the risk of developing cardiovascular disease.[3,4] However, there is no evidence that depression treatment reduces cardiovascular events,[24] and there is an ongoing debate about the added value of screening for depression in patients with CVD.[24,25] Nevertheless, depression in patients with cardiovascular disease is not only associated with clinical outcomes, but also with adherence and poorer health status and impairments to quality of life independent of disease severity.[26]

The association between hypertension and distress found in previous research could be explained by decreased adherence to antihypertensive medication.[10,11] However, although as many as 28.9% of the patients in the current study had an elevated systolic blood pressure of >160 mmHg, there was no significant association with depression, anxiety, and Type D personality. These findings suggest that other factors contribute to poor blood pressure

control in elderly patients with hypertension, at least in primary care. The current findings are in line with the results from Friedman et al., who demonstrated no significant difference in depression and anxiety between normotensive and mildly hypertensive participants.[27] Furthermore, the relatively low prevalence of depression in the current study as well as the lack of an association with elevated systolic blood pressure, is also in accordance with the findings of Wiehe et al. who also did not find a higher prevalence of hypertension in depressive individuals.[28]

A major strength of this study is the relatively large sample size of an unselected, elderly hypertension cohort in the primary care setting. The high prevalence of hypertension indicates that (elderly) hypertension patients represent a large proportion of primary care patients where cardiovascular risk management is recommended.[2]

A limitation of the study is the cross-sectional design, which does not allow to draw conclusions about causation or to evaluate symptoms over time. Furthermore, there were only limited data available on patients who refused participation. It is possible that patients who refused participation were more likely to be depressed and anxious, and more likely to have a Type D personality.[29] Furthermore, the Type D construct as a prognostic indicator for cardiovascular outcomes is the subject of some debate.[30] Initially published studies have reported higher odds ratios for Type D personality as a predictor of mortality and cardiovascular outcomes as compared to more recent studies in which more events were reported, which could possibly imply an overestimation of the effect of Type D personality on mortality or cardiovascular events.[5] Finally, depression and anxiety were measured by means of self-report measures rather than a clinical diagnostic interview. However, the PHQ-9 and the GAD-7 are highly validated instruments with good psychometric properties,[13-16] and self-reported symptoms of depression and anxiety have been shown to predict cardiac morbidity and mortality in cardiac populations.[31,32]

In conclusion, a low prevalence of symptoms of anxiety, symptoms of depression, and Type D personality was found in the current study. Furthermore, this study shows no relation between depression, anxiety, and Type D personality and an elevated systolic blood pressure. Therefore, prospective research in primary care populations with hypertension is needed to evaluate the evolvement of psychological distress in association with hypertension over time, and to study the association between psychological distress, hypertension, and long-term cardiovascular outcomes.

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Chapter 6

Beta-blockers and Depression in Elderly Hypertension Patients in Primary Care

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Abstract

Background and objectives: Previous findings regarding a possible association between beta-blocker use and depression are mixed. To our knowledge there have been no studies investigating the association of beta-blockers with depression in primary care hypertension patients without previous myocardial infarction. The aim of this study was to determine the relation between lipophilic beta-blocker use and depression in elderly primary care patients with hypertension.

Methods: A cross sectional study in primary care practices located in the South of the Netherlands. Primary care hypertension patients without previous myocardial infarction or heart failure (N=573), aged between 60 and 85 years (mean age=70±6.6), were included. All patients underwent a structured interview that included a self-report questionnaire to assess depression (PHQ-9), which was divided in 4 groups (PHQ-9 score of 0, 1-3, 4-8, 9 or higher).

Results: A PHQ-9 score of 0 was more prevalent in non-beta-blocker users versus lipophilic beta-blocker users (46% vs. 35%), a PHQ-9 score of 4-8 was less prevalent in non-beta-blocker users as compared with lipophilic beta-blocker users (14% vs. 25%). A Chi^2 test showed that lipophilic beta-blocker users as compared to non-beta-blockers users were more likely to be in a higher depression category (p=.012). Ordinal regression showed a significant relationship between use of lipophilic beta-blockers and depression (OR=1.60, 95%CI:1.08-2.36) when adjusting for potential confounders.

Conclusion: Our findings show that primary care hypertension patients who use a lipophilic beta-blocker are more likely to have higher depression scores than those who do not use a lipophilic beta-blocker.

Introduction

Worldwide the prevalence of hypertension in the adult population is approximately 26%, and the number of adults with hypertension is expected to increase with 60% by 2025.[1] In a Dutch sample of 591 elderly individuals (60-70 years), hypertension was prevalent in 62%.[2] In the Netherlands, once the diagnosis of hypertension has been confirmed and no secondary causes are indicated, most primary care hypertension patients are treated by a practice nurse in conjunction with the general practitioner (GP).

For hypertension patients with concomitant coronary artery disease (CAD) and/or previous myocardial infarction (MI), beta-blockers are recommended by the current guidelines, while beta-blockers are not first choice treatment of hypertension without concomitant cardiac disease.[3] Although beta-blockers are still popular in primary care, the use has been associated with (severe) side effects including fatigue and fluid retention.[4,5]

There is an ongoing debate whether beta-blockers may lead to depression, but evidence for an association between beta-blocker use and depression is mixed. A recent review concluded that many studies are subject to methodological shortcomings that might explain the mixed findings.[6] However, some recent studies with substantial sample sizes, assessing depression with validated instruments, have not found a clear association between beta-blockers and depression,[7-9] or did even find a reduced risk of depression with beta-blocker use.[10] However, these studies focused on patients with established heart disease, including patients treated with percutaneous coronary intervention (PCI), with angina pectoris,[10] with an implantable cardioverter defibrillator (ICD),[7] or patients who recently had an MI.[9] The results of the study of van Melle et al. showed no association between beta-blocker use at discharge and symptoms of depression at 3, 6 and 12 months, but they found a significant association between beta-blocker use and symptoms of depression before admission to the hospital. This association remained significant even after controlling for confounders such as hypertension and previous MI.[9] To our knowledge, only the study of Luijendijk et al. selected elderly people with and without cardiac disease and/or hypertension.[8] This study found an association between highly lipid-soluble beta-blockers and depression in the first 90 days of use, however, the effect disappeared after 90 days.

To our knowledge there have been no studies investigating the association of beta-blockers with depression in hypertension patients in primary care without a previous MI or heart failure. Because lipophilic beta-blockers are still prescribed frequently in primary care hypertension patients - although current guidelines advocate other medications as first-line treatment - more insight into the possible adverse effects can provide valuable information for clinicians. In the current study, we investigated the association between lipophilic beta-

blocker use and depression in elderly primary care hypertension patients without heart failure or a previous MI, taking into account potential confounders, including the use of benzodiazepines, antidepressants, and other factors such as comorbidities that may impinge on this relationship.

Methods

Participants and study design

Between June 2010 and January 2013, primary care patients aged 60-85 years, with diagnosed hypertension in their medical record, were recruited for this cross-sectional study from five different general practices affiliated with the primary care organization PoZoB. The patient population predominantly lives in a semi-rural area in the Southern part of The Netherlands. Patients were excluded in case of a previous diagnosis of heart failure and/or currently being treated by a cardiologist, a history of severe psychiatric illness other than mood or anxiety disorders, cognitive impairments (e.g. dementia), terminal cancer, insufficient knowledge of the Dutch language, or illiteracy or inability to read due to visual impairments. The study protocol was approved by the Medical Ethical Committee of the St. Elisabeth Hospital, Tilburg.

Study procedure

Eligible patients were selected from the GPs' patient records (n=913), received information about the study via postal mail and were contacted by telephone. In case of informed consent an appointment for an intake at the local GP office was planned. This intake consisted of a structured interview, including patient-reported questionnaires, by a nurse at the local GP's office.

Measurements

Demographic and clinical variables

Information on demographic and clinical variables obtained from purpose-designed questions during the interview included gender, age, marital status, employment, educational level (less than high school education vs. high school education or higher), previous episode(s) of depression, life style habits (BMI, current smoking, alcohol intake). Information on clinical variables obtained from the patients' medical records included MI, peripheral arterial disease, cerebro-vascular accidents or transient ischemic attack (CVA/TIA), type 2 diabetes, and prescribed medication.

Symptoms of depression

The prevalence of depressive symptoms was assessed with the Patient Health Questionnaire 9 (PHQ-9). The PHQ-9 is a self-report questionnaire that consists of nine questions tapping into the DSM-IV criteria for a major depressive episode, with answers indicated on a four point Likert scale with a range of 0-27, with a higher score indicating more (severe) symptoms. The PHQ-9 has been validated in elderly primary care populations, with a cut-off of ≥9 indicative of major depression.[11]

Statistical analyses

Statistical analyses were performed using the IBM Statistical Package for the Social Sciences version 18.0. Lipophilic beta-blocker users were compared with non-beta-blocker users or hydrophilic beta-blockers users (n=13) in the analysis. Chi^2 tests were used to examine differences between groups on nominal variables. Student´s t-tests were used for continuous variables or Welch's t-test when the equal variances assumption could not be met.

Due to non-normality of the outcome variable (PHQ-9 total score), the scores on the PHQ-9 were divided into 4 categories: (1) score of 0 (n=247, 43%), (2) score of 1-3 (n=198, 35%), (3) score of 4-8 indicative of mild depression (n=100, 918%), and (4) score of 9 or higher which is indicative of moderate depression (n=28, 5%).[11] A Chi^2 test was used to examine the unadjusted difference between lipophilic beta-blocker users and non-lipophilic beta-blocker users in PHQ-9 score categories (df=3). Ordinal regression was performed to assess the adjusted relation between lipophilic beta-blocker use and depression (PHQ-9 score categories).[12] Multicollinearity was checked prior to the adjusted ordinal regression using Spearman's Rho. All non-parametric correlations were <.400, indicating no problems with multicollinearity. Furthermore the parallel lines as well as the goodness of fit assumptions for ordinal regression were met. The 4 PHQ-9 score categories were entered into the ordinal regression as dependent variable. The independent variable was lipophilic beta-blocker use and other possible confounders were: Age, female gender, low education (less than high school education), marital status (being single/no partner), being employed, type 2 diabetes, CVA/TIA, COPD/asthma, arthritis, peripheral arterial disease, current smoking, regular alcohol consumption (≥2 glasses a day), history of depression, number of antihypertensive medications, benzodiazepine use, and antidepressant use.

Results

Sample characteristics

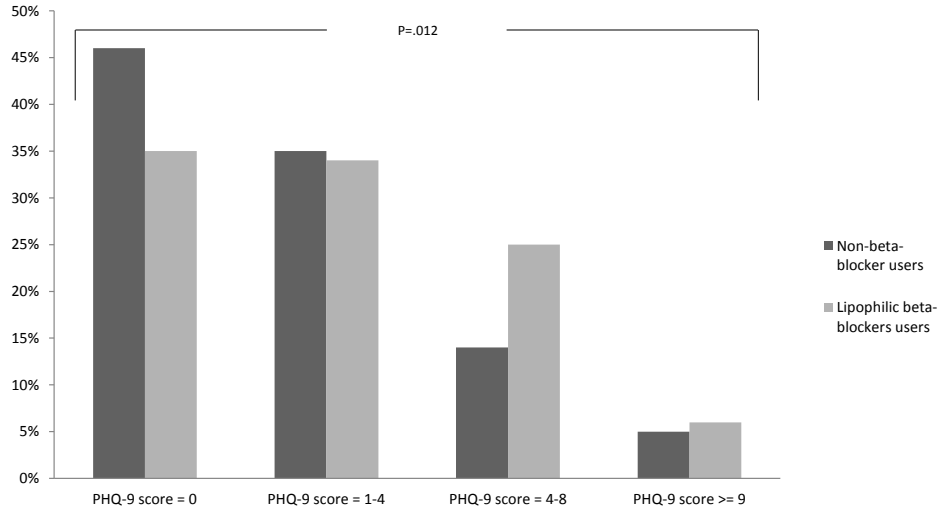
For this study, 913 elderly hypertension patients were approached of whom 619 (68%)

agreed to participate. Another 46 patients were excluded post-hoc because they were currently treated by a cardiologist (n=2), had missing data on medication use (n=6), were not of Dutch origin and had difficulty understanding the Dutch questionnaires (n=11), or had a previous MI (n=27). Finally, 573 patients (63%) were included in the analyses. Table 1 shows that nearly one third (n=164, 29%) of the hypertension patients used a lipophilic beta-blocker (metoprolol, propranolol, bisoprolol, pindolol, carvedilol, nebivolol), with metoprolol being the most frequently prescribed (79%). Patients who used a lipophilic beta-blocker were more likely to use calcium channel blockers (p=.006) as compared to non-beta-blocker users (including 13 hydrophilic beta-blocker users; atenolol, celiprolol, sotalol).

Lipophilic beta-blocker use and depression (unadjusted analysis)

Figure 1 shows that a PHQ-9 score of 0 was more common in the non-beta-blocker users (n=189, 46%) as compared with lipophilic beta-blocker users (n=58, 35%). A score on the PHQ-9 of 4-9 was more common in lipophilic beta-blocker users (n=41, 25%) as compared with non-beta-blocker users (n=59, 14%). Lipophilic beta-blocker use was reported in 24% of the patients with a PHQ-9 score of 0, in 28% of the patients with a PHQ-9 score 1-3, in 41% of patients with a PHQ-9 score 4-8, and in 32% of patients with a PHQ-9 score of 9 or higher (data not shown in table). The overall Chi^2 test showed a significant difference between PHQ-9 categories and lipophilic beta-blocker use (df=3; p=.012).

Figure 1. PHQ-9 scores in categories stratified by lipophilic beta-blocker use



PHQ, Patient Health Questionnaire

Table 1. Baseline characteristics of 573 elderly primary care hypertension patients

Characteristic	*Total, n=573*	*Lipophilic beta-blocker users n=164 (29%)*	*Non-beta-blocker users (including 13 hydrophilic beta-blocker users) n=409 (71%)*	*P-value*
Demographics				
Age, mean (SD)	70 (6.6)	70 (7.0)	70 (6.6)	.325
Men	248 (43%)	67 (41%)	181 (44%)	.458
Low education	73 (13%)	21 (13%)	52 (13%)	.976
Single/no partner	142 (25%)	42 (26%)	100 (24%)	.771
Current employment	71 (12%)	19 (12%)	52 (13%)	.711
Lifestyle and clinical risk factors				
Current smoker	78 (14%)	23 (14%)	55 (13%)	.856
Regular alcohol use (≥ 2 glasses per day)	180 (31%)	45 (27%)	135 (33%)	.194
Mean systolic blood pressure (mmHg), mean (SD)	150 (20.0)	150 (22.6)	150 (18.9)	.913
Mean diastolic blood pressure (mmHg), mean (SD)	82 (11.0)	82 (12.7)	83 (10.1)	.201
Previous depression	75 (13%)	25 (15%)	50 (12%)	.333
Comorbidities				
Peripheral artery disease	20 (4%)	7 (4%)	13 (3%)	.521
TIA/Stroke	49 (9%)	15 (9%)	34 (8%)	.747
Diabetes type II	61 (11%)	17 (10%)	44 (11%)	.891
Asthma/COPD	53 (9%)	11 (7%)	42 (10%)	.183
Arthritis	22 (4%)	2 (2%)	18 (4%)	.269
Medication use				
Diuretics	300 (52%)	93 (57%)	207 (51%)	.187
ACE inhibitors	173 (30%)	40 (24%)	133 (33%)	.055
ARBs	218 (38%)	55 (34%)	163 (40%)	.159
Calcium channel blockers	**103 (18%)**	**41 (25%)**	**62 (15%)**	**.006**
Antidepressants	30 (5%)	12 (7%)	18 (4%)	.157
Benzodiazepines	39 (7%)	12 (7%)	27 (7%)	.759
Hypnotics	5 (1%)	5 (1%)	0	n.a.

TIA, transient ischemic attack; ACE, angiotensin converting enzyme; ARB, angiotensin II receptor blocker

Beta-blocker use and depression (adjusted analysis)

Table 2 shows the results of the ordinal regression analysis with 4 categories of PHQ-9 scores as dependent variable, and age, sex, low education, single/no partner, being currently employed, type 2 diabetes, COPD/asthma, CVA/TIA, peripheral arterial disease, arthritis, current smoking, regular alcohol consumption, history of depression, number of antihypertensive medications, benzodiazepine use, antidepressant use, and lipophilic beta-blocker use as independent variables. In this adjusted analysis, use of lipophilic beta-blockers (OR=1.60, 95% CI:1.08-2.36) was a significant independent associate of depression together with age (OR=.96, 95% CI:.93-.99), female gender (OR=1.68, 95% CI:1.19-2.38), having no partner (OR=2.30, 95% CI:1.55-3.40), asthma/COPD (OR=2.39, 95% CI=1.39-4.11), previous depression (OR=1.64, 95% CI=1.02-2.66), and benzodiazepine use (OR=2.75, 95% CI=1.46-5.17). When examining a dose response relationship between lipophilic beta-blocker use and depression, no significant differences were found between a low dose (below recommended dose) or the recommended dose or higher (data not shown).

Table 2. Adjusted ordinal regression with lipophilic beta-blocker use as independent variable and PHQ-9 categories* as dependent variable in 573 elderly primary care patients with hypertension

	Odds ratio	*95% Confidence interval*
Demographics		
Age	**.96**	**.93-.99**
Female gender	**1.68**	**1.19-2.38**
Low education	1.32	.81-2.15
Single/no partner	**2.30**	**1.55-3.40**
Current employment	0.64	.38-1.10
Comorbidities		
Type 2 diabetes	0.98	.58-1.66
TIA/stroke	0.95	.53-1.70
Peripheral arterial disease	1.04	.43-2.52
Asthma/COPD	**2.39**	**1.39-4.11**
Arthritis	1.09	.47-2.50
Risk factors		
Current Smoking	1.37	.85-2.21
Regular alcohol use (≥ 2 glasses per day)	0.82	.57-1.17
Previous depression	**1.64**	**1.02-2.66**
Medication		
Number of antihypertensive medications	0.99	.82-1.19
Benzodiazepines	**2.75**	**1.46-5.17**
Antidepressants	1.70	.83-3.49
Lipophilic beta-blocker	**1.60**	**1.08-2.36**

*Category (1) score of 0, (2) score of 1-3, (3) score of 4-8, (4) score of 9 or higher.
TIA, transient ischemic attack; COPD, chronic obstructive pulmonary disease

Discussion

Summary of main findings

To our knowledge, this is the first study examining the relationship between lipophilic beta-blocker use and depression in primary care hypertension patients without previous MI or heart failure after adjusting for "classical" associates of depression. This study shows a relation between the use of lipophilic beta-blockers and depression as compared to non-beta-blocker use. Overall, a significant association was found between lipophilic beta-blocker use and symptoms of depression (as divided into 4 categories). Patients with a lipophilic beta-blocker had more often a score on the PHQ-9 between 4 and 9 - indicative of mild depression[13] - as compared with non-beta-blocker users. It is well known that the use of benzodiazepines in the elderly is associated with unrecognized depression may even precede symptoms of depression.[14] Therefore this was an important potential confounder to take into account when looking at an independent association between lipophilic beta-blocker use and depression.[6] Interestingly, diabetes was not associated with depression, which is not in line with previous findings.[15] An association was found between having COPD or asthma and depression, which has previously been reported in a recent meta-analysis.[16]

Strengths and limitations

This study has some limitations. First, the cross-sectional design does not allow for making any inference about cause and effect. Second, although the PHQ-9 is a reliable instrument to assess depressive symptoms,[13] symptoms are not identical to a depressive disorder. Furthermore, fatigue is a common side-effect of beta-blocker use,[17,18] which is also one of the symptoms of depression and included in the PHQ-9.[13] It might be speculated whether the elevated depression scores are a reflection of side-effects related to the use of beta-blockers. However, regardless of the origin of the depressive symptoms, patients in our study using lipophilic beta-blockers reported after adjustment for possible confounders higher depression scores which implies that beta-blockers either are associated with mood directly or produce side effects that contribute to higher depression scores.

This study also has several strengths. To our knowledge, this is the first study to investigate the association of lipophilic beta-blockers with depression in primary care hypertension patients without previous MI or heart failure. As summarized in a recent review, the literature shows rather conflicting results regarding a possible association between depression and beta-blockers, and a majority of these studies had methodological shortcomings, such as using antidepressant treatment as a proxy for depression.[6] However, antidepressants are given for other conditions than depression, including anxiety.[19] Most of the aforementioned methodological shortcomings were all tackled in our study including assessment of

depression with a standardized and validated questionnaire, sufficient sample size, and taking into account confounders that could possibly impinge on the relation between beta-blocker use and depression.

Comparison with existing literature

According to the Dutch primary care guidelines for cardiovascular risk management, beta-blockers are not the primary choice of drug therapy for the treatment of hypertension. Only in case of intolerance to other antihypertensive medications, a beta-blocker should be considered as a sufficient alternative, however, common adverse effects of beta-blockers should be taken into consideration.[20] In our study, 29% of the hypertension patients without a previous MI used a lipophilic beta-blocker, with the majority using metoprolol. Because lipophilic beta-blockers can pass through the blood-brain-barrier, they are most likely to be associated with side-effects associated with the central nervous system such as depression.[18] This was supported by the findings of the current study, as use of lipophilic beta-blockers was associated with increased symptoms of depression. As reported in earlier studies, lipophilic beta-blockers, including the medium lipid-soluble metoprolol which was prescribed most often in our study, can affect the central nervous system resulting in adverse effects such as sleeping problems or changes in mood.[18] Furthermore, previous research showed an association between symptoms of depression and high lipid-soluble beta-blockers. However, this effect was only present in the first 90 days of use and the specific association between medium lipid-soluble selective beta-blockers and depression was not studied because these were taken together with low lipid-soluble beta-blockers in the analysis.[8] In three other studies with reliable assessment of depression, sufficient sample size, and adjustment for other correlates of depression, no association was found between beta-blocker use and depression.[7,9,10] Because these studies included patients with cardiac disease for whom prescription of a beta-blocker is recommended[3,21-23], a possible explanation of the difference in findings could be that in patients with cardiac disease the beneficial effects beta-blockers surpass the adverse effects.

Implications

In conclusion, we found a significant relationship between the use of lipophilic beta-blockers and depression scores in primary care hypertension patients without previous MI or heart failure when adjusting for potential confounders. Our findings underline the recommendation of the most recent guidelines with respect to being cautious with prescribing beta-blockers for the treatment of hypertension in patients without a previous MI or heart failure.

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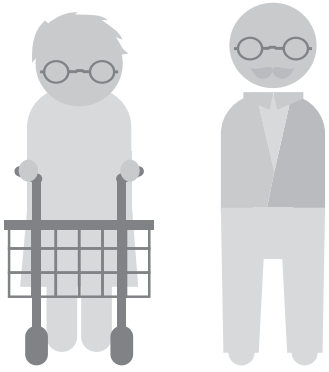
Chapter 7

General Discussion



Background and scope of the thesis

The rationale for this thesis is based on the need to gain insight into the clinical and psychological aspects of hypertension management in elderly patients in primary care. This thesis provides information on how hypertension is currently managed in Dutch primary care, which patients have abnormalities on an echocardiogram, the value of heart failure symptoms in the detection of patients at risk for having cardiac abnormalities on the echocardiogram, and which psychological issues are associated with hypertension and antihypertensive treatment. In this chapter, the main findings of the thesis are summarized, methodological considerations are presented, and implications for clinical practice and future directions are discussed.

Main results and conclusions

Hypertension management and screening in primary care

The Dutch multidisciplinary guideline on cardiovascular risk management (CVRM) describes a target systolic blood pressure (SBP) for hypertension patients of ≤140 mmHg, with the exception of patients aged 80 years an older with a target SBP of ≤160 mmHg, and patients with diabetes with a target SBP of ≤130 mmHg. A progressive stepwise scheme is described with antihypertensive medications to lower SBP. Diuretics are recommended as medication of first choice, with calcium channel blockers (CCB) as second option in case of side effects. However, angiotensin converting enzyme (ACE) inhibitors as well as angiotensin II receptor blockers (ARBs) are equally effective for the prevention of cardiovascular events as compared to CCBs and diuretics.[1] As a second step, a combination of a diuretic and an ACE-inhibitor can be considered, with replacement by an ARB in case of side effects. A third option is the combination of a diuretic with an ACE inhibitor or ARB, and a CCB. Beta-blockers are only recommended in case of side effects to one of the antihypertensive medications described above.[2]

Adequate treatment of hypertension, and therefore adherence to the guideline on CVRM, is important because starting at a SBP of 115 mmHg, an increase of 20 mmHg doubles the risk of cardiovascular morbidity and mortality.[3] We studied the adherence of the GPs from five practices to the Dutch CVRM guideline in 568 primary care patients with hypertension (excluding those with previous myocardial infarction (MI) and/or atrial fibrillation) aged between 60 and 85 years. As indicated by the results presented in *chapter 2*, the majority of these patients (67%) had inadequate blood pressure control according to the Dutch CVRM guideline (SBP>140mmHg, or SBP>130mmHg in patients with type 2 diabetes, or SBP>160 mmHg in patients aged 80 years and older),[2] and 29% of patients had a SBP of >160 mmHg

(stage 2 hypertension[4]). The results showed that only 58% of the patients were managed appropriately according to the guideline. Furthermore, 21% of patients treated according to the guideline had an abnormal echocardiogram compared to 37% who were not treated according to the guideline. In logistic regression analysis, the association between treatment according to the guideline and an abnormal echocardiogram remained highly significant, after adjusting for age, gender, education, current smoking, regular alcohol consumption, body mass index, type 2 diabetes, years since diagnosis of hypertension, and SBP.

American guidelines on CVRM have described that early assessment of cardiovascular risk can enhance individualized efforts to prevent cardiovascular disease.[5] Symptomatic heart failure is generally preceded by asymptomatic cardiac dysfunction or changes in cardiac structure such as left ventricular hypertrophy (LVH).[6,7] According to the current European Society of Cardiology (ESC) guidelines on diagnosis and treatment of chronic heart failure, echocardiography is a useful tool to assess chamber volumes, ventricular systolic and diastolic dysfunction, wall motion, wall thickness, and valvular function.[8] No data are available on the prevalence of abnormal cardiac outcomes in (elderly) primary care hypertension patients. Therefore, the aim of *chapter 3* was to screen primary care patients with hypertension aged between 60 and 85 years for cardiac abnormalities as reflected by an abnormal echocardiogram. The results showed that 30% of patients (n=181) had one or more abnormalities on the echocardiogram. The most prevalent abnormalities were a dilated left atrium (left atrium volume index >29ml/m^2; 10%), reduced left ventricular ejection fraction (<55%; 9%), LVH (6%), and diastolic dysfunction (6%). Older age and a SBP of >160 mmHg were independently and significantly associated with cardiac abnormalities on the echocardiogram.

The feasibility of echocardiography in a primary care setting, the high prevalence of abnormalities on the echocardiogram, and the availability of (simple) interventions imply that screening of elderly hypertension patients by means of echocardiography could be very relevant. However, it is desirable to identify hypertension patients at risk in whom further examination by means of echocardiography is indicated. In the majority of cases the general practitioner (GP) is involved in the initial diagnosis of heart failure.[9] The value of symptoms, such as shortness of breath, fatigue, and edema, for the diagnosis of heart failure seems to be limited.[10] However, previous research mainly focused on patients who were selected because of already existing symptoms[11] and/or did not include all cardiac abnormalities associated with heart failure.[12] To be able to identify patients at risk for cardiac dysfunction, the focus of *chapter 4* of this thesis was to evaluate the diagnostic value of heart failure symptoms (shortness of breath, edema, fatigue, cold extremities and restless sleep) in unselected primary care hypertension patients aged between 60 and 85 years. We showed that in elderly primary care hypertension patients edema of the ankles, feet,

or legs was the most important symptom with a positive predictive value of 45%. Edema was significantly and independently associated with cardiac dysfunction as reflected by an abnormal echocardiogram together with higher age, previous MI, and a SBP of >160 mmHg.

Psychological factors in hypertension in primary care

Currently, psychological distress, such as depression, anxiety, and Type D personality, is receiving increasing attention due to its high prevalence in patients with cardiovascular disease and impact on cardiovascular prognosis.[13] For example, a previous meta-analysis showed that depression is prevalent in approximately 20% of heart failure patients, and is associated with higher risk for morbidity and mortality.[14] Another meta-analysis showed an association between anxiety and higher incidence of coronary heart disease (26%) and higher cardiac mortality risk (48%).[15] Although hypertension patients in primary care represent a large group at risk for cardiovascular disease, research on psychological distress conducted in this patient group is scarce. Furthermore, results of previous research on a possible association between depression and hypertension are inconclusive.[16-19] Therefore, *chapter 5* reported on the prevalence of depression, anxiety, and Type D personality in elderly primary care hypertension patients and examined the relation between elevated SBP (>160 mmHg) and depression, anxiety, and Type D personality. The results showed a prevalence of 5% for depression, 5% for anxiety, and 8% for Type D personality. There was no association between depression, anxiety, and Type D personality and elevated SBP.

Finally, according to the progressive scheme on use of antihypertensive medication in the Dutch guideline on CVRM, the role of beta-blockers has been reduced in comparison with previous guidelines.[2] Several studies have shown inferior effectiveness of beta-blockers as compared to other antihypertensive medication in reducing cardiovascular risk in hypertension patients without previous MI.[1,20] In addition, beta-blockers are associated with (severe) side effects such as fatigue and fluid retention.[21,22] Furthermore, there is ongoing debate concerning the association between lipophilic beta-blockers and depression.[23] Despite the minor role of beta-blockers in the current guideline on CVRM, lipophilic beta-blockers are still frequently prescribed in primary care hypertension patients. Therefore, in *chapter 6* we studied the association between the use of lipophilic beta-blockers and depression in primary care hypertension patients. Our results indicated a significant association between lipophilic beta-blockers and symptoms of depression after adjusting for several possible confounders.

Methodological considerations

Design of the study

In all studies described in this thesis, we used a cross-sectional design, which limits the possibility to draw conclusions regarding causality. Hence, for example we cannot directly conclude that the abnormal echocardiogram as reported in *chapter 3* will result in poorer cardiovascular outcomes as compared to patients with no abnormal echocardiogram. However, previous prospective studies have already unequivocally shown an increased risk of future major adverse cardiovascular events in patients with for example an enlarged left atrium,[24,25] diminished left ventricular ejection fraction,[21], left ventricular hypertrophy,[26] or diastolic dysfunction,[27] which were the most prevalent abnormalities that we found on the echocardiogram. Overall, the results of this thesis should be viewed as preliminary and as a first step in elucidating the potential importance of the current CVRM guideline and a possible inclusion of echocardiography in the standard procedure of CVRM.

Participants and study setting

A large sample of primary care hypertension patients was included in this study (n=619). Patients completed a comprehensive interview including purpose designed questions on demographic information, standardized questionnaires on heart failure symptoms, and standardized and validated questionnaires on psychological distress. The extended focus of the interview and the extensiveness of the information gathered on the participating subjects allowed for controlling for potential confounders. Furthermore, all patients were assessed with echocardiography providing information on cardiac dysfunction. Because patients included in this study were not selected based on signs or symptoms of heart failure, and not treated by a cardiologist, the prevalence of abnormalities on the echocardiogram might be generalized to elderly primary care hypertension patients in general, and not only to those in whom cardiac dysfunction is expected. A study limitation is the limited data available on the non-participants, which hampers the possibility of generalizing our results to the total population of elderly hypertension patients in primary care. However, the majority of patients (70%) approached for study participation agreed to participate, and the available characteristics (age and sex) of the non-participants were similar to the study population, except for the age of the non-participating women, as they were on average 3 years older.

Around the time of inclusion of patients into the study, the participating practices were all starting up a CVRM program. This program aims to prevent (secondary) cardiovascular events and includes structural follow-up by the GP and a practice nurse, multidisciplinary cooperation, and promoting self-management, resulting in an individual care plan for each

patient included in this program. Currently, approximately 45.000 patients are included in the CVRM program of PoZoB, of whom the majority (65%) has hypertension. Since the majority of the patients included in the study as described in this dissertation met the criteria of inclusion in this CVRM program, the sample included in this study can been seen as a subsample representative of the hypertension patients aged between 60 and 85 years included in the CVRM program. Furthermore, the distribution of age and sex were very similar in the study sample as compared with the total population hypertension patients between 60 and 85 years included in the CVRM program of PoZoB.

Measures

Based on previous research, echocardiography is recommended for the detection of both LVH and left ventricular systolic dysfunction in patients at risk for heart failure.[28,29] In our study, a broad spectrum of cardiac dysfunction was found by echocardiography. A strong point of our study is that echocardiography is seen as the gold standard for confirming a diagnosis and establishing the cause of heart failure.[8,21] All the echocardiograms in our study were reviewed by a cardiologist specialized in echocardiography, who indicated if the echocardiogram was abnormal according to a protocol suitable for primary care, based on current echocardiography guidelines.[30,31] The echocardiogram was performed in the local general practice with a mobile echocardiography system, which made the echocardiogram easily accessible to all participating patients. In addition, the costs of such an echocardiogram are not high (€75), enhancing the feasibility of implementing echocardiogram screening as part of the CVRM in general practice.

In the diagnosis of major depressive or anxiety disorder, a diagnostic interview is considered the gold standard. However, a diagnostic interview is expensive and time-consuming. Therefore, in *chapter 5* and *chapter 6* we used the self-report 7-item General Anxiety Disorder scale (GAD-7) and the 9-item Patient Health Questionnaire (PHQ-9) to assess symptoms of anxiety and depression. For the detection of generalized anxiety disorder a cut-off of ≥8 has a high sensitivity and specificity, the area under the curve for detecting generalized anxiety disorder is .91.[32] For the detection of a major depressive disorder as described in *chapter 5,* a cut off of ≥9 was used, since it is considered suitable for elderly individuals in primary care. This cut-off also has a high sensitivity and specificity, and an area under the curve of .87.[33] Both the PHQ-9 and the GAD-7 were developed for use in the primary care setting, and mirror the DSM IV criteria for depressive or anxiety disorder.[34,35] Furthermore, we used categories of depression scores to assess the association between lipophilic beta-blockers and depression. A limitation of our studies in *chapter 5 and 6* was that depressive symptoms are not identical to depressive disorder, as elevated depression scores are not equivalent to having a depressive disorder. Nevertheless, previous research

has shown that approximately 50% of patients with moderate or high scores on the PHQ-9 do have major depression.[36] Lipophilic beta-blocker users had more often depression scores indicative of mild depression, and less often no symptoms of depression in comparison with non-beta-blocker users. Furthermore, several symptoms of depression as described in DSM IV[34] and assessed by the PHQ-9 are very general (e.g. fatigue, problems with sleeping, having trouble with concentrating) and might be explained by side-effects of beta-blockers. It is still unclear whether increased scores on the PHQ-9 are symptoms of depression or a reflection of drug side effects. Future prospective studies are warranted to unravel the association between beta-blocker use and depression in hypertension patients.

Practical and clinical implications

Screening of hypertension patients

The results of the studies described in *chapter 2* and *chapter 3* showed a high prevalence of cardiac dysfunction assessed with echocardiography, with a significant and independent association between cardiac abnormalities on the echocardiogram and SBP as well as an association with treatment according to the current Dutch guideline on CVRM.

According to the guideline for appropriate use of echocardiography, initial and general evaluation of cardiac structure function and routine evaluation of hypertension without symptoms or signs of hypertensive heart disease with echocardiography is discouraged.[37] The use of echocardiography to evaluate suspected hypertension related heart disease is recommended by this guideline.[37] Since the value of symptoms and signs in the diagnosis of heart failure is limited, especially in early stage heart failure, many patients with (early) cardiac dysfunction might not be diagnosed. Whether all hypertension patients of 60 years and older should be screened with echocardiography remains a subject of debate. Only prospective research could elucidate whether patients really benefit from screening. However, benefit from screening is not unlikely when perusing literature on progression from for example LVH or diastolic dysfunction to heart failure. Progression from stage A (only risk factors) and stage B (cardiac dysfunction without symptoms) heart failure to stage C (overt) heart failure is associated with a dramatic (5-fold) decrease in 5-year survival.[6] Furthermore, for example in patients with diastolic dysfunction, ACE-inhibitors and ARBs have been shown to be more effective in improving diastolic filling as compared to other antihypertensive medication.[38] In our study, based on the echocardiogram, the specialized cardiologist not only reported the outcome of the echocardiogram to the GP but also advised the GP when to take further action. For approximately 50% of the patients with an abnormal echocardiogram an advice was given to adapt or change the medication, mainly

consisting of adding or changing to an angiotensin converting enzyme (ACE) inhibitor or to increase the dose of the antihypertensive medication. Other advice consisted of referral to a cardiologist in the hospital setting (24%) or follow-up with an echocardiogram within 1 to 5 years (22%). Moreover, the outcomes of the echocardiogram, including the advice of the cardiologist, were sent automatically to the GP. In every practice, the cardiologist visited at least once during the project to provide the GPs with information on echocardiography and the importance of the most prevalent abnormalities. The participating GPs generally experienced this as a valuable addition to the screening. Furthermore, the results in *chapter 4* showed that patients with edema were at increased risk for having abnormalities on the echocardiogram. Based on these results we can recommend GPs and practice nurses to check for edema and possibly request an echocardiogram in these patients, especially when this is accompanied by elevated SBP.

In the current study, most of the WHO criteria for screening, as indicated by Wilson and Jungner, were met.[39] Overt heart failure is a major health problem,[6] and often preceded by asymptomatic cardiac dysfunction resulting from hypertension such as LVH or diastolic dysfunction.[40] In the focused update of the American Heart Association guidelines for diagnosis and management of heart failure, the importance of early detection of heart failure is emphasized, with the aim of introducing therapeutic interventions before the appearance of left ventricular dysfunction or symptoms in order to reduce population morbidity and mortality of heart failure.[21] Furthermore, echocardiography is important for determining the cause of heart failure as well as to establish appropriate treatment.[8]

Cardiovascular risk management in hypertension

Optimal blood pressure control was only found in a minority of the patients. However, this project was initiated when the CVRM program had just started, underlining the importance of a structured program in which hypertension management plays an important role. It is not unlikely that this program might result in improvements of CVRM in general, as well as specific hypertension management in the near future. A recent report written by the primary care organizations PoZoB and De Ondernemende Huisarts (DOH), who developed the CVRM program together, showed positive preliminary results with 30% of the patients experiencing a decrease in SBP of ≥10 mmHg after 3 years in the CVRM program.[41] It is well known that a decrease of 10 mmHg will result in an absolute risk reduction for cardiovascular events of 22%.[42]

How should we attain systolic blood pressure control?

The World Health Organization stated in "*A global brief on hypertension*" that early detection, adequate treatment, and good control of hypertension is paramount to gain health benefits

and economic benefits.[43] Achieving blood pressure control is important, but generally only observed in approximately 20-54% of hypertension patients as reported in several studies in Europe.[44-47] The Dutch guideline on CVRM specifically emphasizes that patients with inadequate SBP control require the most attention and care.[2] *Chapter 2* depicts that most of the hypertension patients aged between 60-85 years had suboptimal SBP control (71%), and would therefore warrant extra attention and care. Furthermore, 39% of the patients in our sample were not treated according to the current guideline. Although the design of our study does not allow us to draw conclusions about causality, it is at least remarkable that the prevalence of abnormalities on the echocardiogram is 21% in patients who were treated according to the current Dutch guideline versus 37% in patients not treated according to the guideline, with the risk of abnormalities being almost 2-fold. Furthermore, in previous research inadequate treatment has been described to be an important reason for uncontrolled hypertension.[48] This underlines the importance of following the stepwise scheme for antihypertensive medication choice[2] and prescribe adequate dosages. A structured CVRM program including hypertension management could play an important role in achieving better blood pressure control and outcomes in hypertension patients, as supported by previous research. An Australian randomized controlled trial showed that intensive structured care for primary care hypertension patients resulted in significantly better blood pressure control after 26 weeks in comparison with a control group who received usual care.[49] Moreover, a Cochrane review studying interventions used to improve control of blood pressure in patients with hypertension showed the importance of using a systematic approach to deliver care for hypertension, including regular review and intensified antihypertensive drug treatment when necessary. Recently, a report on the PoZoB and DOH CVRM program has indicated that in patients with a SBP of >160 mmHg in whom no decline of SBP of ≥10 mmHg is reached, 25% did not use antihypertensive medication versus 12% in the group with a decline of ≥10 mmHg.[41]

The effect of beta-blocker therapy in treatment of hypertension has been the subject of debate. A review and meta-analysis showed that beta-blockers were (slightly) inferior to other antihypertensive medication in the treatment of hypertension and associated with poorer compliance due to side effects.[20] On the other hand, another meta-analysis found all antihypertensive drug classes to be equally effective, also in patients with hypertension without a history of cardiovascular disease.[50] Irrespectively, beta-blockers remain important in the treatment of patients with a previous MI and/or atrial fibrillation.[51] Taking these findings into account, the guideline on CVRM has given beta-blockers a less prominent role in the treatment of (uncomplicated) hypertension.[2] Although we cannot conclude from the results of *chapter 6* that beta-blockers directly lead to depression, they seem at least associated with elevated depression scores possibly associated with side effects that might

be related to the central nervous system. These findings support the recommendation in the CVRM guideline to be cautious with prescribing beta-blockers as the first-line medication for the treatment of hypertension.

Should we screen for psychological distress in hypertension?

In the European guidelines on cardiovascular disease prevention in clinical practice, psychological distress (including depression, anxiety, and Type D personality) has been described as a contributor to cardiovascular risk as well as to worse prognosis in patients with established cardiovascular disease, and might also be a possible barrier for adherence.[13] Prior findings have shown an independent association between poor medication adherence in elderly patients with hypertension and depression and anxiety, which might be a possible explanation of the association between psychological distress and blood pressure.[52,53] Our results showed a low prevalence of psychological distress and we found no association between depression, anxiety, and Type D personality and elevated SBP. These findings are in line with other previous research that found no association between depression, anxiety and hypertension.[17,19] Furthermore, previous research in primary care diabetes patients not using insulin therapy has shown that the likelihood of depression was doubled but only in patients with multiple vascular co-morbidities, while the prevalence of depression in the patients with one or no vascular co-morbidity was similar to the general population.[54] It seems that higher depression rates might be associated with (multiple) chronic diseases. Moreover, a study in systemic sclerosis patients showed that patients score approximately 1 point higher on the somatic items of the PHQ-9 (fatigue, sleep difficulties, appetite problems, psychomotor agitation/retardation) as compared with non-medically ill respondents.[55] Similar findings were reported in a study with post-MI patients who scored more than one point higher on somatic symptoms of the Beck Depression Inventory in comparison with psychiatric outpatients with no previous MI who were matched on cognitive-affective symptoms scores, sex, and age.[56] The association between depression and cardiovascular outcomes might possibly be explained by disease severity and complications, and therefore be more prominent in patients with established (cardiovascular) disease. Therefore, conventional risk factors as well as severity of the disease should be taken into account in future studies.[57] Our findings do not directly suggest that primary care hypertension patients should be screened for psychological distress. Moreover, there is no evidence that depression treatment reduces cardiovascular events, which in part has led to an on-going debate about the added value of screening for depression in patients with cardiovascular disease.[58,59] Nevertheless, GPs and/or nurses should still be alert and attentive to signs of psychological distress because patients with depression and/or anxiety might be less likely to be compliant with treatment, and psychological distress has a negative impact on overall patient wellbeing and quality of life.[60]

Future directions

One of the most important and general recommendations for future research resulting from this thesis would be to study the course of SBP prospectively within the CVRM program. Future research should focus on the development of heart failure in primary care hypertension patients, taking into account heart failure symptoms as well as cardiac dysfunction as reflected by an abnormal echocardiogram. It might be interesting to study whether patients with a longer duration of elevated SBP, despite being treated for hypertension, would be at greater risk for having cardiac abnormalities on an echocardiogram than patients with a shorter period of elevated SBP. Knowing exactly how hypertension evolves into heart failure would provide valuable information for clinical practice. Furthermore, when keeping the results of *chapters 2* and *3* in mind, a prospective study could provide us with information on whether patients who are treated strictly according to the current Dutch guideline would have better outcomes as compared to those who were not, possibly differentiating between choice of medication and doses of medication. The CVRM program of PoZoB in which nearly 45.000 patients are included might provide prospective data for example regarding treatment according to the guideline in association with outcomes. Prospective research would also be recommended when studying psychological distress as a contributor to cardiovascular risk and/or adherence to antihypertensive medication. However, with the low prevalence and lack of association of psychological distress with elevated SBP in our study, the role of psychological distress in elderly primary care hypertension patients might be small.

Another future direction might be to introduce telehealth to manage hypertension, as self-monitoring of blood pressure might contribute to blood pressure control.[61] Recently, a meta-analysis indicated that better blood pressure control in hypertension patients treated in several different settings using home blood pressure telemonitoring is more likely to be obtained than if patients receive usual care. Blood pressure telemonitoring also resulted in better physical health status in a subset of the studies included in the meta-analysis. Intervention operating costs, however, contributed to significantly higher costs in the group that received blood pressure telemonitoring.[62] Nevertheless, healthcare benefits from lowering SBP, including reducing the risk for cardiovascular disease, would probably become apparent after a longer follow-up period. Recently, similar findings were reported for the effect of home blood pressure telemonitoring in a primary care setting on the short-term (i.e., 6 months follow-up), showing significantly improved blood pressure in comparison with a control group with also higher costs.[63] Future research should reveal the long-term effects of telemonitoring for hypertension patients on blood pressure outcomes, cardiovascular outcomes, health status, and the cost-effectiveness of such an approach.

Concluding remarks

This thesis has shown that almost one third of 'relatively healthy' primary care hypertension patients between 60 and 85 years had clinically relevant abnormalities on an echocardiogram, increasing their risk for developing heart failure. These findings reflect that there is still room for improvement with respect to the management of hypertension in primary care patients aged between 60 and 85 years. Screening of hypertension patients in primary care for echocardiographic abnormalities seems feasible, in particular if a cardiologist advices GPs what further action is required based on the echocardiography results. Echocardiography screening might be a valuable addition to CVRM for hypertension patients, although prospective research is needed to study the effect on cardiovascular outcomes. GPs and practice nurses should be attentive to edema, since this was associated with more abnormal echocardiograms in our study. Furthermore, our findings indicate that screening for psychological distress in primary care hypertension may at this point be premature until further evidence is available from prospective studies, since we found a low prevalence of psychological distress and no association with elevated SBP. This thesis underlines the importance of adherence to the guideline on CVRM. A structured CVRM program - with promising preliminary results - might alter hypertension management and therefore possibly improve cardiovascular outcomes of a large group of primary care patients in the future.

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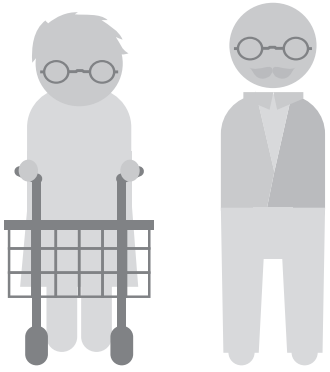
Samenvatting

(Summary)



Inleiding

Hypertensie komt vaak voor, vooral bij ouderen. In de internationale richtlijnen spreekt men van hypertensie bij een systolische bloeddruk van ≥140 mmHg en/of een diastolische bloeddruk van ≥90 mmHg. In Nederland komt hypertensie voor bij 61% van de mannen en 55% van de vrouwen in de leeftijdscategorie 60-70 jaar, oplopend tot ongeveer 70% bij beide in de leeftijdscategorie 70-80 jaar. Hypertensie is niet alleen een belangrijke risicofactor voor het krijgen van een beroerte of een TIA (transient ischemic attack), maar ook voor het ontwikkelen van verschillende hartafwijkingen (o.a. linker ventrikel hypertrofie en diastolische dysfunctie) die bijdragen aan de ontwikkeling van hartfalen (een ontoereikende pompfunctie van het hart). Om te voorkomen dat hypertensie zich ontwikkelt tot hartfalen is goede en gerichte behandeling belangrijk. Deze behandeling, zoals beschreven in zowel internationale richtlijnen als de Nederlandse Multidisciplinaire richtlijn Cardiovasculair Risicomanagement (CVRM), richt zich voornamelijk op het verlagen van de systolische bloeddruk. Systolische bloeddruk is een zeer belangrijke voorspeller van sterfte en het krijgen van cardiovasculaire ziekten, en verlaging van de systolische bloeddruk resulteert in een verminderd risico op het krijgen van cardiovasculaire ziekte of sterfte.

In de afgelopen decennia hebben zich in Nederland verschillende huisartsen-zorggroepen gevormd. PoZoB, met ongeveer 200 aangesloten huisartsen in de regio Zuidoost-Brabant, is één van de grotere zorggroepen in Nederland. In 2010 is PoZoB van start gegaan met een zorgprogramma CVRM. In dit zorgprogramma ontvangen patiënten gestructureerde zorg met als doel het risico op cardiovasculaire ziekte en sterfte te verlagen. Inmiddels zijn bijna 45.000 patiënten met een verhoogd risico en/of cardiovasculaire aandoeningen geïncludeerd in dit zorgprogramma. Het behandelen van hypertensie is hierin een belangrijk onderdeel.

Om inzicht te krijgen in klinische en psychologische aspecten van CVRM bij eerstelijns hypertensie patiënten, wordt in dit proefschrift de evaluatie beschreven van 1) de behandeling van hypertensie, 2) afwijkingen op het echocardiogram en 3) de relatie van deze afwijkingen met symptomen behorende bij hartfalen. Ook is in dit proefschrift gekeken welke psychologische aspecten mogelijk gerelateerd waren aan een matig tot ernstig verhoogde systolische bloeddruk (>160 mmHg). Daarnaast is de relatie tussen bètablokkers en symptomen van depressie onderzocht.

Het onderzoek

Voor het onderzoek beschreven in dit proefschrift zijn ruim 600 patiënten met hypertensie in de huisartsenpraktijk gescreend met de volgende inclusie criteria: 1) leeftijd tussen 60 en 85 jaar oud, 2) geen diagnose hartfalen in het medisch dossier en 3) niet bij een cardioloog onder behandeling. Deze screening gebeurde door middel van een interview op de praktijk waarin vragenlijsten gericht op depressie, angst en Type D persoonlijkheid waren opgenomen. Ook werd het medisch dossier doorgelicht en een echocardiogram gemaakt waarmee hartafwijkingen werden vastgesteld.

Volgens de internationale richtlijnen is het vroeg opsporen van hartafwijkingen en hartfalen cruciaal. Hierbij wordt het echocardiogram gezien als de gouden standaard in het vaststellen van hartafwijkingen behorend bij hartfalen, zoals linker ventrikel hypertrofie. In *hoofdstuk 2* van dit proefschrift is gekeken naar de samenhang tussen het hebben van een afwijkend echocardiogram en hypertensiebehandeling wel/niet volgens de huidige CVRM richtlijn. Deze richtlijn beschrijft welke medicatie gekozen kan worden en wanneer er medicatie zou moeten worden toegevoegd. Bij 38% van de deelnemende patiënten werd de behandeling niet (strikt) volgens de huidige richtlijn uitgevoerd. Deze groep bestond grotendeels uit patiënten die een bètablokker kreeg voorgeschreven. Uit de analyse bleek dat van de patiënten die wel volgens de huidige richtlijn behandeld werd 21% een afwijking had op het echocardiogram, van de patiënten die niet volgens de huidige richtlijn werden behandeld had 37% een afwijkend echocardiogram. Naast het hebben van een hogere leeftijd en/of een hogere systolische bloeddruk, hing het niet worden behandeld volgens de huidige richtlijn onafhankelijk samen met het hebben van een of meer afwijkingen op het echocardiogram.

In *hoofdstuk 3* wordt verder ingegaan op afwijkingen op het echocardiogram. In totaal had 30% van de onderzochte groep een of meer belangrijke afwijkingen op het echocardiogram. Oudere patiënten met een systolische bloeddruk hoger dan 160 mmHg hadden een grotere kans om afwijkingen te hebben op het echocardiogram. De meest voorkomende afwijkingen waren een vergroot linker atrium (10%), verminderde linker ventriculaire ejectie fractie (9%), linker ventrikel hypertrofie (6%) en diastolische dysfunctie (6%). Deze vier categorieën werden gezien bij bijna 75% van de patiënten met afwijkingen op het echocardiogram en bij 22% van de totale groep onderzochte patiënten. Uit de literatuur blijkt dat al deze afwijkingen belangrijke voorspellers zijn voor het krijgen van hartfalen, en dat adequate behandeling dit risico duidelijk verlaagt.

Huisartsen zijn vaak betrokken bij het vaststellen van (beginnend) hartfalen en het is daarom belangrijk om te weten welke symptomen van belang zijn in de signalering van beginnend hartfalen. *Hoofdstuk 4* van dit proefschrift beschrijft de diagnostische waarde

van de symptomen kortademigheid, vermoeidheid, oedeem van de enkels, voeten en/ of onderbenen, rusteloze slaap en koude ledematen voor het hebben van een afwijkend echocardiogram. De resultaten lieten zien dat oedeem het belangrijkste symptoom was met een positief voorspellende waarde van 45% voor hebben van afwijkingen op het echocardiogram.

Bij patiënten met cardiovasculaire aandoeningen is er steeds meer aandacht voor depressie, angst en Type D persoonlijkheid (de neiging om negatieve emoties te ervaren in combinatie met moeite om deze emoties te uiten naar anderen). Voorgaande onderzoeken - voornamelijk in tweedelijns populaties - laten zien dat depressie, angst en een Type D persoonlijkheid vaker voorkomen bij patiënten met cardiovasculaire aandoeningen en daarnaast ook gerelateerd kunnen zijn aan een slechtere prognose. Omdat hypertensie een belangrijke risicofactor is voor het ontwikkelen van cardiovasculaire aandoeningen is in *hoofdstuk 5* gekeken naar de prevalentie van depressie, angst en Type D persoonlijkheid bij oudere patiënten (60-85 jaar) met hypertensie in de huisartsenpraktijk. De resultaten lieten zien dat de prevalentie van depressie (5%), angst (5%) en Type D persoonlijkheid (8%) laag waren. Daarnaast werd er geen samenhang gevonden met het hebben van een verhoogde systolische bloeddruk.

De huidige CVRM richtlijn beschrijft een stappenplan voor de medicamenteuze behandeling van de systolische bloeddruk bij hypertensie patiënten. Bètablokkers zijn antihypertensiva die in de huidige richtlijn geen (eerste) voorkeur verdienen in de behandeling van hypertensie, en slechts worden geopperd in het geval van bijwerkingen van andere eerste keus medicatie zoals ACE-remmers of AII-antagonisten. Bètablokkers kunnen bijwerkingen zoals vermoeidheid veroorzaken en omdat lipofiele bètablokkers de bloed-brein-barrière kunnen passeren zouden ze mogelijk gerelateerd kunnen zijn aan depressieve symptomen. Eerdere onderzoeken laten tegenstrijdige resultaten zien met betrekking tot een mogelijke samenhang tussen het gebruik van bètablokkers en depressie. Omdat deze onderzoeken voornamelijk werden uitgevoerd bij patiënten met cardiovasculaire ziekte werd in *hoofdstuk 6* gekeken naar de samenhang tussen het gebruik van lipofiele bètablokkers en depressie bij hypertensie patiënten in de huisartsenpraktijk. Uit de resultaten bleek dat het gebruik van lipofiele bètablokkers - die nog veel worden voorgeschreven ondanks de bescheiden rol in de richtlijn - onafhankelijk samenhing met depressieve symptomen.

Discussie

Hypertensie is een belangrijke risicofactor voor het krijgen van cardiovasculaire aandoeningen zoals hartfalen, en komt vaak voor bij ouderen. Adequate behandeling zoals beschreven in de Nederlandse multidisciplinaire richtlijn CVRM is daarom van groot belang. Dit wordt onderstreept door resultaten beschreven in dit proefschrift; bijna een derde van de onderzochte groep patiënten had een of meer belangrijke (klinisch relevante) afwijkingen op het echocardiogram. Daarnaast hadden veel patiënten niet de optimale systolische bloeddruk en hadden de patiënten met een hogere systolische bloeddruk en/of die niet volgens de huidige richtlijn behandeld werden een fors hogere kans om afwijkingen te hebben op het echocardiogram. Het onderzoek beschreven in dit proefschrift is cross-sectioneel. Longitudinaal onderzoek zal meer inzicht kunnen geven in hoe de echoafwijkingen zich in de tijd ontwikkelen en wat het effect is van adequate behandeling op het krijgen van cardiovasculaire aandoeningen en het risico op sterfte. Dit proefschrift laat zien dat de prevalentie van depressie, angst en Type D persoonlijkheid laag is bij oudere eerstelijns hypertensiepatiënten. Dit onderzoek geeft geen aanleiding voor extra aandacht voor depressie, angst en Type D specifiek voor oudere patiënten met hypertensie. Echter, bij patiënten die lipofiele bètablokkers gebruiken zou aandacht voor bijwerkingen waaronder symptomen van depressie wenselijk zijn.

Dit proefschrift geeft inzicht in verschillende aspecten behorende bij CVRM voor hypertensie patiënten die in de huisartsenpraktijk behandeld worden. Deze resultaten geven aanknopingspunten voor vervolgonderzoek en mogelijk ook voor de aandachtspunten binnen de behandeling van hypertensie in een CVRM zorgprogramma binnen de huisartsenpraktijk.

Dankwoord

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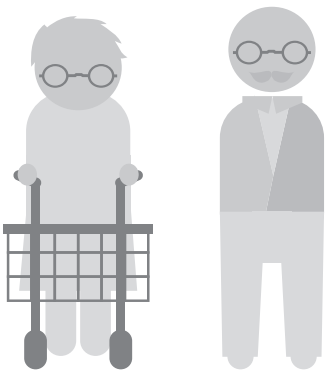

Dankwoord

Na vier jaar hard werken is het tijd voor het laatste stukje van mijn proefschrift; het dankwoord. Er zijn veel mensen die direct of indirect een bijdrage hebben geleverd aan dit proefschrift. In dit dankwoord wil ik een aantal van hen in het bijzonder bedanken.

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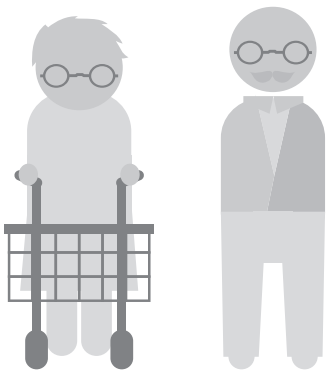
Over de Auteur

(About the Author)



Lianne Ringoir werd geboren op 4 januari 1983 te Eindhoven. In 2001 behaalde zij haar VWO diploma aan het Heerbeeck College te Best. Na het VWO ging ze Psychologie studeren aan Tilburg University, en later aan Maastricht University waar ze binnen de afstudeerrichting Biologische Psychologie haar master Neuropsychology afrondde in 2007. Na haar afstuderen werkte ze als junior onderzoeker en promovendus bij het Trimbos Instituut en de Vrije Universiteit Amsterdam. In 2009 startte ze met haar promotieonderzoek bij het Center of Research on Psychology in Somatic Diseases (CoRPS) bij Tilburg University. Tijdens het uitvoeren van dit onderzoek had ze zowel een werkplek bij Tilburg University als bij zorggroep PoZoB in Veldhoven. Op dit moment is Lianne werkzaam bij PoZoB als projectmanager.

Lianne Ringoir was born on the 4th of January 1983 in Eindhoven, The Netherlands. In 2001 she graduated from high school at the Heerbeeck College in Best. After high school she studied psychology at Tilburg University and subsequently at Maastricht University with a specialization in Biological Psychology and she finished the Master Neuropsychology in 2007. After obtaining her degree she started working as a junior researcher and PhD-student at the Trimbos Institute and VU University Amsterdam. In 2009 she started as a PhD student at the Center of Research on Psychology in Somatic Diseases (CoRPS) at Tilburg University. During the conduction of her research she had a workplace both at Tilburg University and PoZoB (Veldhoven). At present, Lianne works as a project manager at PoZoB.